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SEROUS OTITIS MEDIA

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Serous otitis media is arousing increasing interest among otologists, partly because the incidence of the disease seems to have grown and partly because its treatment in many cases affords difficult problems If left untreated, it changes into chronic adhesive otitis and resultant severely impaired hearing Treatment must be started before irreversible changes have occurred in the tympanum and the eustachian tube Chronic cases of serous otitis media which are often refractory to all conventional therapy can be successfully treated by an indwelling plastic tube in the tympanum The latent mastoiditis which frequently accompanies the condition must first be cured

Serous otitis media has been called "a challenge to otolaryngology" (Hoople, 1950) The disease is by no means new as early as 1862 Politzer described its symptoms and treatment Serous otitis media has also been described as otosalpingitis, tubal catarrh, catarrhal otitis media, secretory otitis media, exudative otitis media, otitis media with effusion, etc Many authors believe that the incidence of serous otitis media has increased in recent years (Hoople & Blaisdell, 1943, Suchs, 1952, Harcourt & Brown, 1953, Singleton, 1956 Theobald, 1958, Senturia *et al* 1958) It occurs in conjunction with occlusion of the eustachian tube

Anatomy

The eustachian tube, which in adults is 35 mm long, leads from the nasopharynx to the middle ear It is a vestigial remain of the first pharyngeal pouch The tympanal portion of the tube is surrounded by bone and forms one third of the total length The pharyngeal portion is surrounded by cartilage and opens into the lateral wall of the nasopharynx, the ostium is surrounded by a cartilagenous rim called the torus tubarii The narrowest part of the tube, at the junction of bone and cartilage, is called the isthmus

The epithelial lining of the tympanum is largely composed of simple non-ciliated cuboidal cells which have no basement membrane As the mucosa extends posteriorly to the aditus ad antrum, the antrum and the mastoid air cells, the cuboidal epithelium is gradually transformed into simple squamous and the mucosa becomes extremely thin and endothelium like. ...embrane is also coated with simple

squamous epithelium. There are no glands in the submucosa, but in certain conditions of inflammation gland-like mucus producing areas are formed in the mucosa (Beck 1926, Singer 1932). The lumen of the tube is lined with ciliated pseudostratified columnar epithelium, which towards the tympanum gradually becomes lower and assumes the character of tympanic epithelium. The movements of the cilia are directed towards the nasopharynx.

Physiology and Pathology

The lumen of the cartilaginous portion of the tube is normally closed but opens physiologically on swallowing. The muscular action of the tube is produced by the tensor veli palatini and the levator veli palatini, which pull apart the anterior and posterior lips of the torus and simultaneously shut off the nasopharynx from the oropharynx. The act of swallowing produces a slight transient overpressure in the nasopharynx, which in physiological conditions cannot increase. For normal ventilation of the middle ear the tube must be opened by this physiological overpressure. If for some reason the tubal mucosa swells, this overpressure is not always enough to open the tube, and as a result the middle ear becomes a closed space; air is absorbed by the mucosal blood vessels, and underpressure occurs. Resorption of air continues until an equilibrium is reached between the partial pressure of air gases in the blood and in the middle ear. The partial pressure of air gases bound in the blood is about 950 cm H_2O, the atmospheric pressure *equals about 1000 cm H_2O. The resorption of air from the middle ear* therefore results in an underpressure of about 50 cm H_2O. Van Dishoeck (1941) was able to demonstrate, by means of his pneumophone, that maximum underpressure does in practice equal about 50 cm H_2O. The greater the underpressure in the middle ear, the greater the overpressure required in the nasopharynx to open the tube. After the underpressure has persisted for some time it produces an irritation of the mucosa in the middle ear, resulting in oedema and metaplasia. Subsequently transudation and exudation fill the middle ear with effusion, and with simultaneous absorption the effusion gradually becomes thicker.

Etiology

Effusion originates in connection with an occlusion of the eustachian tube. It seems clear, however, that not all conditions of tubal occlusion are accompanied by effusion in the middle ear (Zollner 1936, van Dishoeck 1941, Carpenter 1949, Hopple 1950). Other contributory factors are apparently required to occur. Several authors consider that the most important contributory *cause is mild infection* (van Dishoeck 1941, Carpenter 1949, Robison & Nicholas 1951). The present writer also believes that infection is the most important contributory factor. Other authors have held that allergy plays an important part (Hoople & Blaisdell 1943, Dohlman 1943, Derlacki & Shambaugh 1953, Solow 1958, Jones 1959). Yet in cases in

which allergy is present it is often difficult to overlook the role of infection since an allergic mucosa is highly susceptible to and hard to rid of infection. There is also a risk that one assumes an allergic etiology merely because no other causative factor is demonstrable.

Serous otitis media is mostly seen in connection with adenoid hyperplasia. The disease also accompanies chronic rhinitis, latent mastoiditis, sinusitis, deformities of the septum, cleft palate, nasopharyngeal neoplasms, metabolic disorders and dental malocclusion. The present writer has in addition been able to diagnose serous otitis media in some cases of chronic bulbar palsy, where the nasopharynx cannot be closed and the pharynx often reveals infected burns. There are, however, cases of serous otitis media in which the reason for the tubal occlusion remains undetected.

The incidence of serous otitis media is highest among young children, evidently because this is the age group in which *upper respiratory tract* infections are most common and which is predisposed to tubal occlusion by hyperplastic adenoids. Inadequate antibiotic therapy for prophylactic purposes in simple respiratory tract infections may be the reason for the *development* and persistence of many cases of serous otitis media. Many instances of the chronic form of the disease also occur in latent mastoiditis (Robison 1942, Hitschler 1955, Goodhill 1958, Grahne 1964).

Symptoms

Patients often have a feeling of fullness and heaviness *in the ear, frequently* associated with tinnitus. Autophony is also often noted. The *hearing loss is* of the conductive type and the difficulty in *hearing, together* with a simultaneous *mild earache*, often follows a common cold. In cases of serous otitis media among *children*, the child becomes generally more irritable. The patients show no pyrexia and do not feel ill.

Otoscopy *often reveals* a yellow coloured tympanic membrane with a greasy appearance. Sometimes it is *brownish* or pearly in colour. Some retraction of the tympanic membrane is usually present. With Siegle's pneumatic otoscope it can be seen that the mobility of the tympanic membrane is restricted. *Myringotomy* will show that the tympanic cavity contains effusion that is more or less slow *moving* and if this is aspirated the *patient's* hearing is dramatically restored to normal. Effusion may also be present within the tympanic portion of the eustachian tube, in the antrum and mastoid air cells. The fluid may be serous, *mucoid* or glue like in consistency. It is often almost colourless *with a yellow* or grey, or occasionally a bluish or brownish tint. The disease usually *occurs* bilaterally. The Rinne test will be negative. In unilateral cases the Weber will lateralize to the affected ear. A pure tone audiogram often shows a conductive loss of 20–30 db, though sometimes an even heavier loss of hearing may be revealed. A false

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also results from an increased mass. Diagnostic myringotomy with simultaneous aspiration of effusion should be performed. In many cases of chronic serous otitis media the X-ray picture will show a sclerotic mastoid process.

Although several authors have been able to demonstrate the presence of bacteria in the effusion (Lorschner 1925, Blegvad 1931, King 1953, Senturia *et al.* 1958) the effusion is generally sterile (Scheibe 1889, Hoople & Blaisdell 1943, Shahinian 1943, Lystam 1954, Theobald 1958, Lemon 1962). This fact is somewhat bewildering since a mild infection is often a simultaneous finding. Many cases of serous otitis media certainly represent aborted acute otitis media, which without antibiotic therapy would have involved suppurative ears. The latent mastoiditis which fairly often occurs in the chronic cases is also bacterial in character (Grahne 1964). The bacteriostatic effect of exudate in acute otitis media has been demonstrated by Siirala & Lahikainen (1952) and by Siirala & Vuori (1954). It may be assumed that the effusion in serous otitis media has a similar effect and as a result bacteria cannot generally be shown.

Treatment

Serous otitis media, as stated above, is most common among young children. The problem here is usually simple and connected with the presence of adenoid hyperplasia. Once adenoidectomy with simultaneous myringotomy and aspiration of the effusion is performed, the problem in a vast majority of cases is solved. It is of importance even in cases in which adenoidectomy has been performed earlier to consider a possible regrowth of adenoid tissue in the nasopharynx. A reabrasion is then required (Hass 1961). X-ray and radium therapy have long been practised to reduce the hyperplastic lymphoid tissue in or near the orifices of the eustachian tube. Day wrote in 1950 that we are rapidly reaching the point when cures are worse than the disease, and the beneficial effects of irradiation will be overshadowed by the deleterious and destructive results of its injudicious use. The present writer was unable to observe any improvement of the symptoms in 3 cases of chronic serous otitis media in which the tubes had been treated with X-ray therapy.

Most of the other known reasons for tubal occlusion as listed above are also eradicable by suitable measures. Particularly obstinate symptoms from the upper respiratory tract and the ears occur in children with chronic bronchitis. Chronic bronchitis has recently acquired increased interest because of the augmentation of the impurities in the air which is assuming the character of an ever greater social problem (Birath 1962). It is to be expected that the otologists will have increasingly difficult problems to solve in the treatment of the sequelae which will arise in this context.

Considerable difficulties are connected with the treatment of patients who suffer from serous otitis media in its chronic form. The reason for tubal occlusion is in such cases often obscure, and the conventional methods of removing the tubal occlusion have not be[illegible]

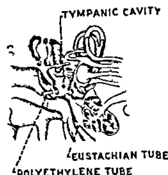


Fig. 1. The flanged tube in position with one end in the tympanum and the other in the ear canal.

1962) has described a method of treating such obstinate cases as these. One end of a small plastic tube is inserted in the tympanum through a myringotomy opening. The air then passes through the plastic tube into the *tympanic cavity* and pressure differences will be levelled. The tube is left in position until the eustachian tubes resume their normal function. The use of plastic indwelling tubes has also been briefly mentioned by other authors (Goodhill 1957, 1958; Burton & Wright 1961; Bell 1961; Boor, 1962; Lemon 1962).

The present writer (1964) published a report on the results of tube treatment in chronic serous otitis media which had proved refractory to all conventional therapy. The series consisted of 25 patients and the total of affected ears was 43. For 14 patients the treatment had been completed and freedom from symptoms reached within an observation period of not less than 8 months. The duration of tube treatment in this group averaged 8.2 months. For 11 patients the tube treatment had been introduced in the immediately preceding 8 months and was still continuing. During the course of treatment all the patients were completely symptom free and felt no inconvenience whatever from the polyethylene tube. Fig. 1 shows the tube in position.

An X-ray of the mastoid process will show sclerosis and arrested pneumatization in many cases of chronic serous otitis media. In order to discover whether a latent mastoiditis is present in such cases an explorative mastoidectomy is required. It is surprising that a latent mastoiditis can quite often be revealed in this way: in Grahne's series (1964) this was demonstrated in 12 out of 31 ears. The histological picture of the granulations seen on mastoidectomy shows distinct signs of a creeping latent inflammation (Fig. 2).

The present writer first performs mastoidectomy post-auricularly. A polyethylene drain is then introduced into the antrum and the skin and the periosteum are sutured exactly above the mastoidectomy cavity. The drain is removed 8 days after the operation. The end result is that a large air-filled space is formed in the middle ear. It comprises the tympanum which, via the aditus, is connected to the mastoidectomy cavity; this latter has smooth walls which are gradually covered by a thin mucosa. The proportion of air

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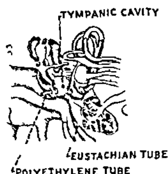


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Fig. 2. Specimen of granulations from the antrum showing distinct signs of a creeping inflammation with fibrosis, glands coated by atrophic epithelium and foreign body reaction with cholesterol crystals. Hemalaun-eosin staining. × 120.

to mucosal surface in this air-filled space is considerably greater than preoperatively. The resorption of air into the blood is therefore slower and this gives relief to the eustachian tube. If symptoms of serous otitis media recur after mastoidectomy the polyethylene tube must be inserted through the tympanic membrane. Latent mastoiditis is not detected in all the cases in which mastoidectomy is performed on the above indications, but even so the operation improves conditions in the middle ear.

In some cases of serous otitis media the effusion is so thick that tympanotomy is required before the glue-like matter can be removed (Colman 1958, Bauer & Wodak 1961, Grahne, 1964).

If serous otitis media is not treated or cannot be cured it will gradually develop into chronic adhesive otitis, as was pointed out by *Politzer* as early as 1867 and subsequently by other authors (Lumio, 1951, Ojala, 1953, Siirala, 1960). Armstrong (1962) believes that cholesteatoma can develop in serous otitis media through mucosal metaplasia. He reports on 2 cases in which this was assumed to have occurred, but his assertion is difficult to understand and the present writer has observed nothing of the kind. On the other hand, there are cases in which an invagination of the pars flaccida, due to underpressure, has formed the basis for the development of a cholesteatoma.

ZUSAMMENFASSUNG

Die Otitis media serosa hat in letzter Zeit immer mehr das Interesse der Otologen auf sich gezogen, und zwar erstens weil die Frequenz der Krankheit gestiegen zu sein scheint und zweitens weil die Therapie in vielen Fällen vor schweren Problemen steht Bleibt die Krankheit unbehandelt, so geht sie in chronische adhäsive Otitis über, die schwere Gehörsminderung zur Folge hat Die Behandlung sollte einsetzen ehe irreversible Veränderungen im Tympanum und in der Tuba Eustachii aufgekommen sind Die chronischen Fälle von Otitis media serosa, die oft jeder herkömmlichen Behandlung trotzen, können erfolgreich so behandelt werden dass man im Tympanum durch eine Inzision im Trommelfell das mit einer Manschette versehene Ende einer kleinen Plastiktube einführt Die nicht selten gleichzeitig bestehende latente Mastoiditis muss zuvor geheilt werden

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FULL THICKNESS SKIN GRAFT FOR CLOSURE OF TYMPANIC MEMBRANE PERFORATIONS

Follow up Investigation of 140 Cases

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During the years 1959 1960 156 patients have undergone tympanoplastic operation type I using retroauricular skin 140 of these cases have been followed up with an observation time of between 2½ and 4½ years

In 60 per cent there has been a primary healing A control examination about 4 years later showed the healing to be 33 per cent This figure will probably be still lower as many transplants have more or less dermatitic changes

In those cases where primary or secondary myringoplastic operations have been a failure secretion granulations in the middle ear and cholesteatoma can often be seen

The operation results show a tendency to be poorer in course of time and a failure of the transplantation may even be dangerous for the operated ear It is the author s opinion that external skin should not be used as a graft in middle ear operations

INTRODUCTION

In 1874 Thiersch showed that large skin defects healed quicker and better if autoplastic skin was transplanted to the granulation bed Berthold (1878) admitted that it was this that prompted him the same year to attempt to close two tympanic membrane defects with full thickness skin from the arm He called the procedure myringoplasty Nine similar operations were reported by Ely (1881) and two by Tangemann (1884) The preliminary results were promising However Berthold (1889) was less optimistic as regards the long term results The method fell fairly soon into disuse

When Zöllner and Wullstein introduced the tympanoplastic procedures in the nineteen fifties skin predominated as material for tympanic membrane grafts Zöllner (1951) and Moritz (1952) initially recommended pedicled full thickness skin grafts But Wullstein (1952) preferred free retroauricular full thickness skin a view later also adopted by Zöllner (1953) Seenola (1955) showed the retroauricular skin to be structurally closer to the tympanic membrane than other skin Wright (1956) and Guilford *et al*

(1958, 1959) also advocated the use of retroauricular skin, but expressed the view that it should be of three quarter thickness—as the circulation in the graft would then be better since more capillaries would be open towards the tympanic bed. Beickert (1958) and Schuknecht (1960) drew attention to the late complications—consisting in cholesteatoma, cellulitis, and perforation—which attend skin grafting in general and split-skin grafts in particular. Wullstein (1960) again stressed the superiority of retroauricular full thickness skin, as it lacks hair and its glands do not extend down into the subcutis. This rules out severed epithelial slips as the cause of secondary epithelial cysts in the graft. Pesavento (1960) compared full thickness and split skin grafts for tympanic membrane repair and considered the full thickness skin graft to be the better as it is more resistant to infection and secondary cholesteatoma. On the other hand, Allen *et al.* (1960) found full thickness skin to afford poorer postoperative hearing than the thinner split skin graft.

Owing to the disadvantages of full thickness skin grafts, mentioned above, an increasing number of otologists have in recent years abandoned them for different connective tissues. Guilford (1962), for instance, held that skin from the exterior of the body as a tympanic membrane substitute was a thing of the past, and Thorburn (1963) expressed the view that extrameatal skin was not to be recommended as a graft. However, Wullstein (1963) still preferred free full thickness skin in the repair of large perforations, and Kley (1963) maintained that full thickness skin was of value as coverage for a deeper fascial graft.

The continued divergence of opinions as to the suitability of full thickness skin in middle ear grafting prompted me to carry out the follow up investigation reported below.

MATERIAL

The patients in this follow up series were collected from the Departments of Otology in the Northern Swedish towns of Boden and Umeå, and include only those coming to surgery in 1959 and 1960.

As the study was aimed chiefly at ascertaining the manner in which full thickness skin grafts reacted as tympanic membrane substitutes in the long run, the only cases of relevance were those in which the operative procedure was limited to the tympanic membrane, that is, cases of myringoplasty and tympanoplasty I. Patients with, for instance, a radical cavity were not included.

The choice of operative method was in the individual case governed by analysis of the clinical condition, tubal function, prosthetic test, and the audiogram. Total dryness of the involved ear for at least one month was a preoperative requirement. The operative procedure itself was that in current use: excision of the edges of the performation and the epithelium removed from the remnants of the drum and possibly from the adjacent portions of the auditory canal. In the presence of tubal perforation, in particular, the auditory canal was widened with a drill as suggested by Guilford *et al.*

(1959) The full thickness grafts used were of retroauricular skin in roughly half the cases these were free grafts as proposed by Wullstein and in half pedicled as suggested by Salen (1961)

Altogether 156 patients were operated upon in this manner during the two year period covered by the investigation Of these 140 have now been followed up The mean interval between operation and follow up was just under 4 years

A check up of the same series in 1961 showed that some 60 per cent of the perforations were closed at that time between 3 and 27 months had elapsed since the operation

RESULTS

Retroauricular full thickness skin was then used for myringoplasty or tympanoplasty I (according to Wullstein) in 140 patients who were followed up The closure of the perforation was excellent in 26 cases (18 per cent) The hearing of most of these patients was improved although total deafness developed on the treated side in one patient Although the tympanic membrane defect was closed in a further 21 patients (15 per cent) they are instead suffering from myringitis cholesteatoma and the like Hearing was improved in just under half these cases In 93 instances (67 per cent) the operation failed entirely to secure closure of the middle ear Forty five of these patients have since come to reoperation chiefly on other principles Among the remaining 48 patients in whom the perforation persisted secretion from the middle ear was noted in every third case In this group of patients with persisting defects who have not undergone reoperation hearing improved in one third and was impaired in one third in the remaining third hearing remained unaltered No definite difference emerged between pedicled and free grafts in the present series

Table 1 gives the whole series of patients treated with myringoplasty or tympanoplasty I during 1959 and 1960 It will be seen that of the 140 patients followed up 47 showed closure of the perforation that is 33 per cent of the follow up series Seventy two of the 140 patients followed up had been treated with free grafts and 68 with pedicled grafts In the first group 2? of the 72 grafts took and in the ...
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TABLE 1 *Myringoplasty or tympanoplasty I with retroauricular full th[illegible] 1959 and 1960*

Interval preceding follow-up at least 2¾ and at most 4¾ [illegible]

Total No of cases	Followed up	Closure	Failure
156	140	47 (33 %)	9[illegible]

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Altogether 156 patients were operated upon in this manner during the two-year period covered by the investigation. Of these, 140 have now been followed up. The mean interval between operation and follow-up was just under 4 years.

A check-up of the same series in 1961 showed that some 60 per cent of the perforations were closed; at that time between 3 and 27 months had elapsed since the operation.

RESULTS

Retroauricular full-thickness skin was then used for myringoplasty or tympanoplasty I (according to Wullstein) in 140 patients who were followed up. The closure of the perforation was excellent in 26 cases (18 per cent). The hearing of most of these patients was improved, although total deafness developed on the treated side in one patient. Although the tympanic membrane defect was closed in a further 21 patients (15 per cent), they are instead suffering from myringitis, cholesteatoma and the like. Hearing was improved in just under half these cases. In 93 instances (67 per cent) the operation failed entirely to secure closure of the middle ear. Forty-five of these patients have since come to reoperation, chiefly on other principles. Among the remaining 48 patients, in whom the perforation persisted, secretion from the middle ear was noted in every third case. In this group of patients with persisting defects who have not undergone reoperation, hearing improved in one third and was impaired in one third; in the remaining third hearing remained unaltered. No definite difference emerged between pedicled and free grafts in the present series.

Table 1 gives the whole series of patients treated with myringoplasty or tympanoplasty I during 1959 and 1960. It will be seen that of the 140 patients followed up, 47 showed closure of the perforation, that is, 33 per cent of the follow-up series. Seventy-two of the 140 patients followed up had been treated with free grafts and 68 with pedicled grafts. In the first group 21 of the 72 grafts took, and in the second group 26 of 68 grafts healed. However, the interval preceding follow-up was on the average six months longer in the free than in the pedicled graft group.

TABLE 1. *Myringoplasty or tympanoplasty I with retroauricular full thickness skin in 1959 and 1960*

Interval preceding follow-up at least 2 [illegible] and at most 4 [illegible] years

Total No. of cases	Followed up	Closure	Failures
156	140	47 (33 %)	93 (67 %)

TABLE 2. *47 cases with postoperative closure of the tympanic membrane defect*

Graft resembling tympanic membrane 26			Graft resembling skin 21		
Hearing	improved	17	Hearing	improved	9
	impaired	1		impaired	2
	unchanged	8		unchanged	10

Table 2 gives the hearing in the cases in which the graft took—either developing into a structure resembling tympanic membrane or retaining its character of full thickness skin. In the 17 cases showing amelioration and in which the graft had the appearance of tympanic membrane, air conduction increased on the average from 41 to 22 decibels and the air bone gap decreased from 30 to 11 decibels. The loss of hearing in one instance was due to sudden labyrinthitis three weeks after the operation, leading to total deafness.

In the group of 21 cases in which graft retained its full thickness skin character, hearing improved in nine instances in which the air conduction increased as a rule from 38 to 24 decibels and the air bone gap decreased from 27 to 15 decibels. In the two patients whose hearing deteriorated, air conduction decreased from 28 to 34 decibels and the air bone gap increased from 27 to 31 decibels. The negligible change in the air bone gap was due to a postoperative increase in nerve deafness at 2000 cps. Myringitis was demonstrated in 18 of the 21 patients in this group, being accompanied by an auditory canal cholesteatoma in seven cases, by granulations in three cases, and by an epidermoid cyst in the graft in one case. In three instances the skin like graft showed no superficial changes whatever, although there was a distinct adhesive tendency in two of them.

Table 3 lists the 93 cases in which the tympanic membrane perforation persisted postoperatively. Of these patients 45 had undergone reoperation before the present follow up study was carried out and could consequently not be analysed. As will be seen in Table 3, hearing had in fact improved in 12 of the 48 patients who were not reoperated on. Air conduction increased on the average from 43 to 30 decibels and the air bone gap decreased from 32 to 18 decibels. In the twelve patients whose hearing deteriorated, air

TABLE 3. *93 cases in which the tympanic membrane defect persisted postoperatively*

Not reoperated 48			Reoperated 45
Hearing	improved	12	
	impaired	12	
	unchanged	14	
	obscure	10	

conduction fell from 36 to 48 decibels and the air–bone gap *increased from* 24 to 34 decibels Ten patients were assigned to a group headed obscure, in these cases the initial audiograms had been *incomplete The* 48 patients not coming to reoperation who were, therefore, available for analysis included 17 in whom there was secretion *the secretion was accompanied by* auditory canal cholesteatoma in four cases, by a cholesteatoma of the middle ear in three, by an epidermoid cyst *in remnants of* the graft in one, and by middle ear granulations in three cases

DISCUSSION

At the start autoplastic full thickness skin was reported to give excellent results *for closure of tympanic membrane defects However, as the interval* preceding follow up lengthened and the number of cases increased optimism *waned This is illustrated in some measure by* Table 4

A check up in 1961, when between 3 and 27 months had elapsed since the operation showed the perforation to be closed in 60 per cent of cases This figure agrees well with most of the results listed in Table 4 But in 1963, when the interval between operation and follow up had increased by 2½ years, the number of ears showing closure had fallen to just over 30 per cent This figure is close to the result published by Mawson *et al* (1962) However this cannot be taken to be the true end result, as in some 50 per cent of the cases in the present series in which the perforation was rated as closed the graft still had the character of external skin Dermatitis, cellulitis, and epidermoid cyst may well lead to future perforation in several instances The only cases which can be regarded as truly healed are those in which the skin *graft has* wholly been replaced by connective tissue later covered by epithelium advancing from the auditory tube This applies in only 18 per cent of the present series It seems that some of these late perforations might

TABLE 4 *Proportion of perforations closed following full thickness skin grafting in the relevant literature*

Author	Year	No of cases	Interval preceding follow up	Closure of perforation %
Guilford	1959	154	> 3 months	63
Brandlow	*1960*	*300*[a]	> 3 years	94
Agazzi	1960	212	1 to 2 years	75
House *et al*	1961	*111*	?	65
Mawson *et al*	1962	67	1 to 5 years	44
Wright	1963	195[b]	?	66
Portmann	1963	*300*	?	65

[a] 1400 patients operated upon of which 300 selected at random
[b] ⅔ split thickness skin

TABLE 2 *47 cases with postoperative closure of the tympanic membrane defect*

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Mawson *et al*	1962	67	1 to 5 years	44
Wright	1963	195[b]	?	66
Portmann	1963	300	?	65

[a] 1400 patients operated upon of which 300 selected at random
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be delayed or prevented by regular local therapy for years after the operation. The tendency to dermatitis should decrease if the desquamation debris is continually removed. Cholesteatoma and retention cysts in the graft should be removed before they have attained a size leading to perforation. Regular after-care was found to be required in a major series (Bandtlow 1960). This author recorded ears without secretion postoperatively in 82 per cent of cases kept under regular surveillance, while the corresponding figure for patients not so frequently examined was 34 per cent. It is undesirable *and often difficult to get post-myringoplasty patients to undergo these regular checks* and they are at least as unpleasant as repeated acid cautery. The patients who in the present series attended for follow-up have therefore been examined only fairly sporadically. Another reason for the difficulty of carrying out postoperative examinations more than twice a year is the long distances to the hospitals in the North of Sweden.

It seems that the reasons why external skin adapts itself so poorly to the *tympanic membrane frame are many. The individual epithelial cell* has fairly high metabolism. According to Laskin *et al.* (1953) it is about 100 times that of a cartilage cell. Furthermore, the density of cells in a skin graft is much greater than in a connective tissue graft. These factors may demand more of the vascular supply than can be offered by a piece of skin suspended over an air-filled cavity. The warmth and humidity deep in the auditory canal in conjunction with the poor oxygenation of the graft create conditions favouring the development of dermatitis, cellulitis and the like. Further, the cellular migration necessary to the removal of debris, noted by Simson (1936) in the auditory canal skin, is lacking in the epithelium of the extra-meatal skin. As, moreover, preformed epithelial tubes in the form of glandular ducts are present, it follows that both infection and epithelial proliferation may extend to the middle ear. Link (1960) also suggested that auto-antigens formed by the breakdown of cells might play some part in the failure of the skin graft. According to Billingham (1956) the antigenic properties of the skin are in fact bound to the nuclei of the epithelial cells. Therefore an interesting point is that the "maladie de la greffe", which commonly occurs, disappears when the epithelial part of the graft has been sloughed. The bradytrophic corium, on the other hand, is accepted far more readily.

CONCLUSIONS

As emerges in earlier reports, myringoplasty with full-thickness skin has been regarded as affording postoperative closure of the perforation in more than 60 per cent of cases. But the favourable results were probably due to excessively short intervals between operation and follow-up. This is exemplified in the present series, in which the proportion of closures was found on early follow-up to be around 60 per cent. But in 1963, when a further 2½ years had elapsed, follow-up of the same series showed closure of the perforation in only 33 per cent of cases. It should also be noted that the closure

of the perforation was fully satisfactory in only just over half this 33 per cent of cases while in the remaining instances the graft—although intact—was diseased and perforation may supervene sooner or later

The lesions fairly frequently noted in ears in which myringoplasty has failed are of interest Several of these ears which were dry prior to the operation and had normal middle ear mucosa on follow up showed cholesteatoma in the auditory tube or middle ear myringitis in remnants of the graft or granulative middle ear changes

As the number of perforations increases with a lengthening interval after operation and as an unsuccessful full thickness skin graft in many instances impairs the condition of the treated ear it is the author s view that extra meatal skin should not be used as a graft for tympanoplasty

ZUSAMMENFASSUNG

In den Jahren 1959 1960 wurde an den Ohrenkliniken in Boden und Umeå bei Myringoplastik Tympanoplastik I retroaurikulare Haut in 156 Fallen angewandt Davon wurden 140 nachuntersucht Die Beobachtungszeit variierte zwischen 2¾ und 4¾ Jahren

Primar gegluckte Resultate sind bei ca 60 % der Falle vorgekommen Nach durchschnittlich knapp 4 Jahren Beobachtungszeit ist jedoch diese Zahl auf 33 % gesunken Sie wird vermutlich weitersinken dagegen die Halfte der verheilten Transplantaten ihren Charakter von oft dermatitisch veranderter Oberhaut behalten

In den Fallen in denen die myringoplastischen Eingriffe entweder primar oder sekundar missgluckten wurden relativ oft Sekretion Mittelohrgranulationen und Cholesteatom beobachtet Da das Operationsergebnis dahin neigt dass es sich mit verlangerter Beobachtungszeit verschlechtert und da eine missgluckte Transplantation nicht ganz ungefahrlich fur das operierte Ohr ist ist der Verfasser der Meinung dass Oberhaut nicht fur Transplantationen im Mittelohr angewandt werden sollte

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University of Umeå, Sweden

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A STUDY OF THE ORDER EFFECTS ON TRACINGS MADE WITH A BÉKÉSY TYPE AUDIOMETER

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The effects of fixed frequency tracing orders at 4000 cps upon thresholds in quiet in noise and in recovery after noise exposure were determined on a Bekesy audiometer with 32 normal hearing adult subjects The results showed that

1 In the pulsed/continuous tracing order in quiet the difference in threshold sensitivity was non significant Conversely, in the continuous/pulsed tracing order in quiet the pulsed trace threshold was significantly more acute

2 Order effects were present also in the noise tracings Post rest pulsed tones were more acute than pre rest continuous tones However, the converse was not true

3 Tracing order effects were operating in the recovery thresholds Post rest pulsed recovery thresholds were more acute than pre rest continuous recovery thresholds Also, initial thresholds in quiet appeared to have a significant effect on subsequent recovery thresholds for continuous tone tracings This finding did not obtain for pulsed tones

4 When initial thresholds in quiet were compared with recovery thresholds non significant differences obtained for pulsed but not for continuous tones The latter were poorer, which reflects physiological fatigue

5 Implications of the findings were discussed

INTRODUCTION

The development of the vacuum tube pure tone audiometer in 1921 (7) made possible more precise psycho physical experiments in audition However after the introduction of the Bekesy audiometer in 1947 (1) other variables not encountered in manual testing were apparent Some of these variables which have been studied include sources of variations at threshold (3 15 16) rate of attenuation (3 4 6 15 17) comparison of manual and Bekesy thresholds (2) recording table speeds (2 8 13) variability in size of excursions (5 15 16) methods of instruction (17) and sophisticated vs unsophisticated listeners (17) etc

No previous investigators to our knowledge have compared the effects of various orders of presentation of continuous tones and pulsed tones on threshold tracings in quiet in low level noise and in recovery However

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Kopra (11) studied the effects of high level noise stimulation upon Bekesy tracings. Also, Jerger (10) reported on the diagnostic usefulness of Bekesy audiograms using the interrupted/continuous tonal order, although he reported no rationale for the selection. Apparently, other workers have employed either a continuous stimulus or, when varying order of presentation, have followed the pattern selected by Jerger. Although Jerger (10) suggests that the key to fruitful diagnosis is a comparison between continuous and interrupted tracings, he is referring to and utilizing only one order of tonal presentation. The effects of other orders might also provide useful information for an understanding of normal as well as pathological hearing.

When fixed frequency threshold tracings are used to assess auditory function, a knowledge of tonal presentation order effects is imperative. There appears to be a paucity of such information even relative to normal hearing.

It is, therefore, the purpose of this study to examine the effects, if any, of the different orders of tonal presentation on normal hearing adults under various threshold conditions. The specific questions asked in this investigation were:

Are there any differences:

1. In fixed frequency threshold tracings in quiet at 1000 cps as a function of tonal presentation order?
2. In fixed frequency threshold tracings in low level noise at 1000 cps as a function of tonal presentation order?
3. In fixed frequency threshold tracings in recovery from low level noise at 1000 cps as a function of tonal presentation order?
4. In fixed frequency thresholds between initial thresholds in quiet and recovery thresholds following low level noise stimulation at 1000 cps as a function of tonal presentation order?

EXPERIMENTAL PROCEDURE

Instrumentation

Automatic audiometer. A commercial Bekesy type audiometer (Grason Stadler, Model E 800) was employed for automatically tracing thresholds. This instrument has two speeds. With the fast speed two octaves are traversed per minute. Attenuation is at the rate of 5 db per second. The slow speed covers one octave per minute and attenuates at 2.5 db per second. The latter speed was selected for this investigation. An electronic switch in the audiometer could be used to pulse the test stimulus at the rate of 2.5 interruptions per second. A steady uninterrupted tone can also be produced. The instrument was calibrated to a TDH 39 receiver in a MX 41/AR cushion. The earphone was suspended in a spring type headband along with a matching earphone for the ear opposite to the one under test. A switch activates the motor driven attenuator to decrease the intensity of the signal when the key is depressed (tone "just heard") and to increase the intensity of the signal when the key is released (tone "just not heard"). The loudness of the tone

increases continuously as long as the thumb switch is released and decreases as long as the switch is pressed In this way the subject executes a continuous tracing of his threshold sensitivity which is manifested by a series of excursions above and below tonal perception By means of a screw gear a writing pen records the changes in attenuation between just heard and just not heard tones on an audiogram chart moving at 1 4 inches per minute

Noise generator and bone oscillator A Grason Stadler sound generator, Model E5539A was utilized for generating thermal noise The noise generator was appropriately matched to a Hewlett Packard attenuator Model 350 A which permitted attenuation of the noise to any desired level The range of attenuation was 110 db in one and 10 db steps The attenuator in turn was matched to a Radioear bone oscillator number B 70 The bone oscillator suspended in a conventional head band was placed in the center of the forehead Hence the noise for masked thresholds was delivered by bone conduction to each subject It was of sufficient magnitude to shift the air conduction threshold approximately 40 db by earphones Special care was taken to isolate the bone from the air conduction headband by inserting a layer of foam rubber between the two

Testing suite All tests were conducted at the Hearing Clinic of the Kansas University Medical Center in a sound treated two room suite consisting of a control room and a test room with an observation window between the two The Bekesy type audiometer was located in the control room The test room contained the earphones bone oscillator and a chair for the subject The ambient noise level in this room as measured with a General Radio sound level meter and an Octave Band Analyzer was less than 26 db re 0 0002 micro bar on the C scale for the octave bands 600 1200 1200–2400 2400 4800 and 4800 9600 cps The room was therefore adequate for threshold measurements

Subjects

The subjects for this investigation were graduate and undergraduate students of the Kansas University Medical Center and Rockhurst College The experimental group consisted of 16 males and 16 females whose age range was 18 to 24 years with a mean age of 22 years 10 months None of the subjects had any previous experience or practice in executing threshold tracings on a Bekesy audiometer

The tests were confined to one ear per subject with the selection of the better ear as the test ear All subjects in this study had hearing thresholds of 15 db re American audiometric zero or better in the test ear In addition to normal or better sensitivity in the test ear all subjects reported an absence of ear pathology family history of hearing loss and significant exposure to loud sounds

Test Administration

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Test Administration

Each subject was individually trained for the hearing tests The standard instructions for the Initial Threshold in Quiet (ITQ) treatment were modified from those suggested by Jerger (10)

A 30 second practice session with the 1000 cps test tone preceded all test runs. Preliminary experimentation had shown that approximately 30 seconds were required for the threshold to stabilize and for the listener to get the feel of the situation. Although each trial lasted 3.5 minutes, data were recorded only during the last three minutes of each trial.

If the subject was following directions at the end of the 30 second practice period, the Bekesy attenuator pen was set on the starting line for the first Initial Threshold in Quiet (ITQ) tracing. On completion of the first tracing a hand signal was given to the subject which indicated that the other tone would then be presented to him. A 30 second practice period was given for the new signal, and the second ITQ tracing was plotted with that signal. The two Initial Threshold in Quiet tracings, therefore, immediately followed each other but were separated by a 30 second practice session with the second signal.

On completion of the continuous and pulsed tone Initial Threshold in Quiet tracings, the subject was reinstructed to listen for the presence of the pure tone in a background of noise. Following instructions, the white noise and the pure tone signal were simultaneously introduced into the bone oscillator and earphone, respectively. Again, 30 seconds of practice ensued to provide threshold stabilization. Then the attenuator pen was set on the starting line for the first Masked Threshold (MT) tracing. After the 3 minute tracing in the noise, the aforementioned noise was abruptly terminated and the direction of the audiogram carriage bound reversed. Thereupon the Recovery Threshold (RT) was recorded continuously for 5 minutes.

Following the first MT-RT tracing the subjected waited for one hour before exposure to additional testing. Since hearing was tested in one ear only, an hour rest interval was arbitrarily selected to allow recovery from the effects, if any, of the preceding low level noise stimulation. After the one hour rest period, all subjects were reinstructed on the threshold tracing in noise and subsequent recovery. The second MT-RT treatment, preceded by a 30 second practice session, was then administered with the alternate stimulus signal. Although each noise-recovery trial lasted 8.5 minutes, data were recorded only during the last 8 minutes of each trial. The administration of all treatments required approximately one hour and 45 minutes.

In summary, the experimental procedure was as follows: Initial Threshold in Quiet (ITQ) tracing, Masked Threshold (MT) tracing, and Recovery Threshold (RT) tracing, each with a continuous and pulsed tone. The latter two treatments occurred either before or after a one hour rest interval. All thresholds are reported in decibels re 0.0002 microbar.

Scoring

Reliability. Various methods of calculating mean threshold values of Bekesy type audiometric tracings have been used by researchers, but only two methods were considered in this investigation. Since no published

research was found reporting the reliability of the various methods utilized in calculating threshold values a preliminary investigation was conducted to determine reliability With one method the mean of each excursion for the 30 second time interval is found and the mean of the means computed The results are reported in decibels as the mean of an arbitrarily selected time period With the other or mid point method threshold is computed by connecting the mean of the first excursion with the mean of the last excursion of the 30 second time period by a line Threshold is determined by finding the decibel value where the line crosses the half way point of the 30 second tracing

A preliminary analysis was conducted using both measuring methods with 16 threshold tracings made by four subjects The difference *in* the means of the two methods was statistically non *significant Therefore* since the mid point method was found easier and faster to calculate it was selected for use in the study

Scoring of thresholds Measurements of the three treatments which *were of* particular concern in this investigation were as follows

1 Initial Threshold in Quiet (ITQ) This is operationally defined as the best pure tone threshold at 4000 cps without any prior stimulation other than environmental noise Calculation of mean thresholds *for the* 32 *ears* was made from two arbitrarily selected 30 second *time periods after 0 5 and 2 5 minutes* of listening These absolute thresholds are reported in *terms of* sound *pressure level (SPL)* in decibels re 0 0002 microbar Two measure*ments each* were taken both for the continuous and pulsed tone tracings for each subject

2 Masked Threshold (MT) Masked Threshold is *operationally defined* as the elevated threshold resulting from low level bone-conducted thermal noise stimulation Calculation of the mean thresholds *for the* 32 ears was made from two arbitrarily selected 30 *second time periods* after 0 5 and 2 5 minutes of listening in low level *noise* These thresholds are reported in terms of sound *pressure* level (SPL) in *decibels* re 0 0002 microbar Again two measurements were taken *both for the* continuous and pulsed tone tracings for every subject

3 Recovery Threshold (RT) Recovery *Threshold* is operationally defined as the threshold in *quiet after* termination of *thermal noise* stimulation Mean thresholds for the tracings of *the* 32 *ears were calculated* from three arbitrarily selected 30 second periods of *the 5 minute recovery trace* after 1 0 2 5 and 4 5 minutes of listening These thresholds are *reported* in terms of sound pressure level (SPL) in decibels *re* 0 0002 microbar Three measurements each were taken both for *the continuous* and pulsed tone tracing for every subject

The mean curves for the 14 arbitrarily selected measurements and the four orders of tonal presentation *are shown* in Fig 1 Preliminary statistical tests of the differences between *threshold values* in each treatment indicated that none was significant *Therefore to facilitate* analysis of the data the

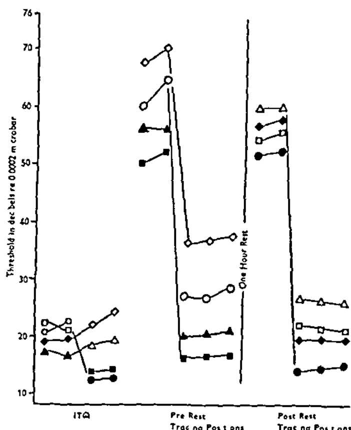


Fig. 1. Mean curves in decibels re 0.0002 microbar at discrete measuring periods for the four orders and three treatments.

	Tracing orders	Symbols
1	ITQ(C)—ITQ(P)—MT(C) RT(C) R—MT(P) RT(P)	(C P – ●)
2	ITQ(C)—ITQ(P)—MT(P) RT(P) R—MT(C) RT(P)	(C – P ■)
3	ITQ(P)—ITQ(C)—MT(P) RT(P)— R—MT(C) RT(C)	(C P ▲)
4	ITQ(P)—ITQ(C)—MT(C) RT(C)—R MT(P) RT(P)	(C – ◇ P ◆)

means in each treatment were averaged. The new means were the average of the means of the last one half minute of the first and third tracing minutes of the Initial Threshold in Quiet (ITQ) and Masked Threshold (MT) treatments, and of the first one half minute of the second tracing minute and the last one half minute of the fifth tracing minute for the Recovery Threshold (RT) treatments. Thus, results are reported relative to six individual mean thresholds for each order of tonal presentation.

RESULTS

Over-all Treatments

Pulsed tones. The means of the pulsed tone tracings for the three treatments and the four orders of tonal presentation are summarized and graphed in Fig. 2. An analysis of variance, designated by Lindquist (14, pp. 281–284) as a Type III design, was performed.[1] The two main effects, ITQ Orders

[1] Tables showing the results of analysis of variance as well as *t* tests are not presented in this paper to reduce the number of tables. These analyses may be obtained from the authors.

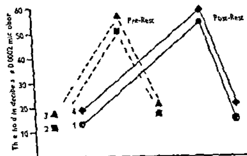


Fig 2 Mean pulsed (P) tone tracings for the over all treatments—Initial Threshold in Quiet (ITQ) Masked Threshold (MT) and Recovery Threshold (RT) treatments—for the four orders of tonal presentation Means are in decibels re 0 0002 microbar

	Tracing orders	ITQ	MT	RT
1	ITQ(C)—*ITQ(P)*—MT(C)-RT(C)—R—*MT(P)-RT(P)* ●	13 50	52 50	14 88
2	ITQ(C)—*ITQ(P)*—*MT(P) RT(P)*—R—MT(C)-RT(C) ■	13 38	51 62	16 50
3	*ITQ(P)*—ITQ(C)—*MT(P) RT(P)*—R—MT(C) RT(C) ▲	18 00	56 62	21 25
4	*ITQ(P)*—ITQ(C)—MT(C) RT(C)—R—*MT(P) RT(P)* ◆	19 00	58 12	21 12

and Treatments (ITQ MT and RT) were significant at the 0 01 level of confidence As shown in Fig 2 thresholds for the pulsed tones were more acute following rather than preceding the continuous tracings (plots 1 and 2 compared to plots 3 and 4) The analysis indicates then that the pulsed ITQs varied as a function of tonal presentation order Similarly, threshold levels varied as a function of treatments i e, in quiet, in noise, and in recovery No other effects were significant

Continuous tones The means of the continuous tone tracings for the three treatments and the four orders of tonal presentation are summarized in Fig 3 The results of the analysis of variance designated by Lindquist (14) as a Type III design indicated that two main effects were significant The differences between the pre rest and post rest Masked Threshold–Recovery Threshold (MT RT) orders were significant at the 0 05 level of confidence The findings are apparent in Fig 3 As would be expected the Treatments (ITQ MT and RT) were significantly different at the 0 01 level of confidence In addition the interaction between treatments and MT–RT tracing orders as well as the interaction between treatments and ITQ tracing orders were significant at the 0 05 level of confidence However ITQs for the continuous tones did not differ significantly as a function of order In other words threshold sensitivity for continuous tones did not change as a result of the preceding or succeeding pulsed tone tracing Yet the pre rest and post rest MTs for the continuous tones differed with the latter (post rest MTs) showing significantly less shift under the noise stimulation Similarly there appears to be a significant difference in pre rest and post rest RTs with the latter appearing more sensitive

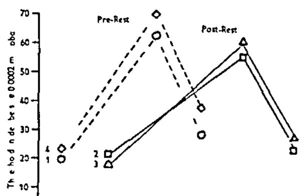


Fig. 3. Mean continuous (C) tone tracings for the over all treatments—Initial Threshold in Quiet (ITQ), Masked Threshold (MT), and Recovery Threshold (RT) treatments—for the four orders of tonal presentation. Means are in decibels re 0.0002 microbar.

	Tracing orders	ITQ	MT	RT
1	*ITQ(C)*—ITQ(I)—*MT(C)* *RT(C)*—R—MT(I) RT(I)	21.88	63.00	28.75
2	*ITQ(C)*—ITQ(I)—MT(I)-RT(I)—R—*MT(C)* *RT(C)*	21.25	55.88	23.12
3	ITQ(I)—*ITQ(C)*—MT(I) RT(I)—R—*MT(C)* *RT(C)*	19.25	60.62	26.75
4	ITQ(I)—*ITQ(C)*—*MT(C)* *RT(C)*—R—MT(I) RT(I) ◇	23.62	69.25	37.75

Initial Threshold in Quiet (ITQ) Treatment

The means and standard deviations for the two ITQ orders traced with continuous and pulsed tones are presented and plotted in Fig. 4. An analysis of variance designated by Lindquist (14, pp. 267–273) as a Type I design indicated that the main effect for Stimulus Tones was significant at the 0.01 level of confidence. The main effect for Tracing Orders was non significant. However, an interaction between the Stimulus Tones and Tracing Orders was significant at the 0.05 level of confidence.

To examine the differences between the mean continuous and pulsed tone thresholds, *t* tests for two related samples were computed (12, pp. 305–308). The results of this analysis showed that when pulsed tone tracings followed continuous tone tracings in ITQ treatments, the differences in thresholds were significant at the 0.05 level of confidence. The differences between the two thresholds in the converse ITQ tracing order were not significant.

Masked Threshold (MT) Treatment

The means and standard deviations for the four pre rest and the four post rest MT tracings with the continuous and pulsed tones are presented in Fig. 5.

The results of the analysis of variance, designated by Lindquist (14) as a Type III design, revealed that the three main effects of this analysis were significant. Stimulus Tones and the ITQ Orders were significant at the 0.01 level of confidence. The differences between the pre rest and post rest Masked Threshold Recovery Threshold (MT–RT) orders were significant

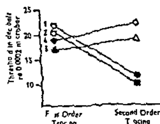


Fig 4 Means and standard deviations for the Initial Threshold in Quiet (ITQ) treatments for the continuous (C) and pulsed (P) tone tracings for the four orders of tonal presentation Means are in decibels re 0 0002 microbar

Tracing orders	Cont tones		Pulsed tones	
	Mean	S D	Mean	S D
ITQ(C)—ITQ(P) (C = ○ P = ●)	21 88	8 80	13 50	3 50
ITQ(C)—ITQ(P) (C = □ P = ■)	21 25	6 28	13 38	4 50
ITQ(P)—ITQ(C) (P = ▲ C = △)	19 25	7 22	18 00	4 30
ITQ(P)—ITQ(C) (P = ◆ C = ◇)	23 62	6 40	19 00	5 48

at the 0 05 level of confidence The interaction between Stimulus Tones and MT–RT Orders (pre rest or post rest tracing position) was significant at the 0 05 level of confidence None of the other effects of this analysis was significant

The differences in mean continuous and pulsed tone pre rest and post rest MTs following the two ITQ tracing orders were tested for two related samples *(12)* The results of this analysis showed that the post rest MTs for pulsed tones were significantly more sensitive than the pre rest MTs for continuous tones Conversely, post rest MTs for continuous tones were not significantly

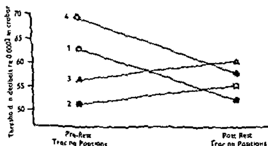


Fig 5 Means and standard deviations *for the Masked Threshold* (MT) treatments for the continuous (C) and pulsed (P) tone tracings for the *four orders* of tonal presentation Means are in decibels re 0 0002 microbar

Tracing orders	Cont tones		Pulsed tones	
	Mean	S D	Mean	S D
ITQ(C)—ITQ(P)—*MT(C)*-RT(C)—R—*MT(P)* RT(P) (C = ○, P = ●)	63 00	8 79	52 50	4 18
ITQ(C)—ITQ(P)—*MT(P)*-RT(P)—R—*MT(C)*-RT(C) (P = ■, C = □)	53 88	4 86	51 62	5 54
ITQ(P)—ITQ(C)—*MT(P)*-RT(P)— R—*MT(C)* RT(C) (P = ▲, C = △)	60 62	9 07	56 62	7 76
ITQ(P)—ITQ(C)—*MT(C)* RT(C)— R—*MT(P)* RT(P) (C = ◇, P = ◆)	69 25	7 66	58 12	5 62

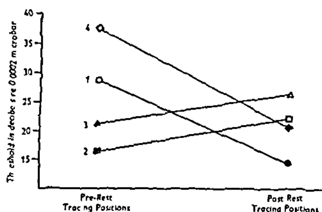


FIG. 6. Means and standard deviations for the Recovery Threshold (RT) treatments for the continuous (C) and pulsed (P) tone tracings for the four orders of tonal presentation. Means are in decibels re 0.0002 microbar.

	Tracing orders	Cont. tones Mean	Cont. tones S.D.	Pulsed tones Mean	Pulsed tones S.D.
1	ITQ(C)—ITQ(P)—MT(C)—*RT(C)*—R—MT(P)—*RT(P)* (C ○—P ●)	28.25	11.55	14.88	1.84
2	ITQ(C)—ITQ(P)—MT(P)—*RT(P)*—R—MT(C)—*RT(C)* (P ■—C □)	22.12	6.47	16.50	5.81
3	ITQ(P)—ITQ(C)—MT(P)—*RT(P)*—R—MT(C)—*RT(C)* (P ▲—C △)	26.25	5.21	21.25	4.46
4	ITQ(P)—ITQ(C)—MT(C)—*RT(C)*—R—MT(P)—*RT(P)* (C ◇—P ◆)	37.75	14.51	21.12	4.91

different from pre-rest MTs for pulsed tones. These findings are clearly illustrated in Fig. 5. Hence, a statistically significant order effect associated with MTs contingent upon either pre-rest or post-rest tracing positions was operating in MTs.

Recovery Threshold (RT) Treatment

The means and standard deviations for the four pre-rest and the four post-rest RTs traced with continuous and pulsed tones are presented in Fig. 6. The results of the analysis of variance, designated by Lindquist (14) as a Type III design, showed that the three main effects of this analysis were significant. The Stimulus Tones and the ITQ Orders were significant at the 0.01 level of confidence. MT-RT Orders were significant at the 0.05 level of confidence. However, none of the interactions was significant.

To evaluate the significance of the differences between the mean continuous and pulsed tone thresholds, *t* tests for two related samples (12) were computed. The results showed that the post-rest pulsed tone RTs were significantly more sensitive than the pre-rest continuous tone RTs at the 0.05 level of confidence. Conversely, continuous tone post-rest RTs were not statistically different from the pre-rest pulsed tone RTs.

Temporary Threshold Shift

Temporary threshold shift is operationally defined as the deviation in decibels from an individual's own previously established audiogram. It is,

TABLE 1 Means and differences between the means of the Initial Threshold in Quiet (ITQ) and Recovery Threshold (RT) treatments for continuous (C) and pulsed (P) tones for the four orders of tonal presentation Summary of t tests testing differences between the treatments as a function of stimuli

Tracing orders	Cont tones			Pulsed tones		
	RT	ITQ	Diff	RT	ITQ	Diff
1 ITQ(C)—ITQ(P)—MT(C) RT(C)—R—MT(P)-RT(P)	28 25	21 88	6 37[a]	14 88	13 50	1 38
ITQ(C)—ITQ(P)—MT(P)-RT(P)—R—MT(C)-RT(C)	22 12	21 25	87	16 50	13 38	3 12
3 ITQ(P)—ITQ(C)—MT(P) RT(P)—R—MT(C)-RT(C)	26 25	19 25	7 00[a]	21 25	18 00	3 25[b]
4 ITQ(P)—ITQ(C)—MT(C)-RT(C)—R—MT(P)-RT(P)	37 75	23 62	14 13[a]	21 12	19 00	2 12

[a] Statistically significant at the 1 % level [b] Statistically significant at the 5 % level

therefore a measure of change in status of hearing as a result of an intervening stimulus The decibel difference between the initial threshold and the recovery threshold is the amount of temporary threshold shift

Table 1 summarizes the differences between mean ITQs and mean RTs for the continuous and pulsed tones traced during the four orders of tonal presentation These differences were tested with a *t test for related samples* (12) *It will be noted* from the table that in three out of four instances the continuous tone recovery thresholds were significantly less sensitive than their *corresponding* ITQs In regard to the pulsed tones however only one of the *four differences* was significantly less sensitive in the recovery treatment than in the corresponding ITQ treatment Apparently the masking noise had a *more* pronounced fatiguing effect upon the RTs of the continuous tones than *upon* the RTs of the pulsed tones

DISCUSSION

ITQ Treatment

The reader will recall that there were *significant* differences in threshold sensitivity in quiet between the *continuous* and pulsed tone tracings as a function of tonal presentation order However differences were significant only in the tracing order in which the continuous tone preceded the pulsed tone When pulsed tones preceded continuous tones the thresholds were not statistically different The fact that the pulsed/continuous tracing order in quiet produced mean thresholds which were statistically identical supports Jerger s (10) clinical procedure at least for the test frequency of 4000 cps and confirms the classification of a Type I Bekesy audiogram However when the converse or
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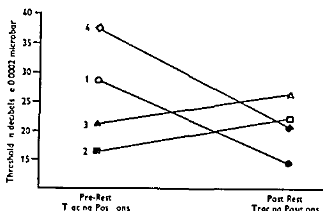


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3	ITQ(P)—ITQ(C)—MT(P) *RT(P)*—R—MT(C) *RT(C)* (P = ▲, C = △)	26.25	5.21	21.25	4.40
4	ITQ(P)—ITQ(C)—MT(C) *RT(C)*—R—MT(P) *RT(P)* (C = ◇, P = ◆)	37.75	11.51	21.12	4.91

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The findings of the current study tend to indicate that a continuous tone stimulus somehow sensitizes or alerts the organism so that a succeeding

pulsed tone is perceived at a more acute threshold level. The pulsed tone, however, does not sensitize the organism to an ensuing continuous tone in a similar manner. One interpretation relative to this finding might pertain to some sort of physiological change in the auditory system contingent upon stimulus order. This change may in some way be related to an alerting mechanism. Another interpretation, however, of a psychological nature is that the subject shifts his response level. In short, he is now responding at the threshold of audibility rather than at the threshold of tonality. The postulation then would be that the shift was triggered by the preceding continuous tone. Seemingly, a continuous threshold tracing preceding a pulsed threshold tracing has the same effect upon the subject in evoking the threshold of audibility as instructions (9).

MT Treatment

As pointed out in the results section, there was an order effect associated with continuous and pulsed tone MT tracings. Specifically, the order effect was related to the comparison between continuous and pulsed MT tracings before and after rest. Significant threshold differences were found only when the pre-rest MTs for continuous tones preceded the post-rest MTs for pulsed tones. In the converse MT order, differences were non-significant.

However, when the MTs for the pulsed tones were compared without regard either to pre-rest or post-rest tracing positions, the amount of shift in noise appears to be related to the HTQ values. For example, on the one hand, pulsed tone MTs of 51.62 db and 52.50 db were preceded by pulsed tone HTQs of 13.38 db and 13.50 db, respectively. On the other hand, the MTs of 56.62 db and 58.12 db followed HTQs of 18.00 db and 19.00 db. More acute pulsed tone HTQ tracings were followed by more acute pulsed tone MT tracings, and less acute HTQ tracings were followed by less acute MT tracings. Hence, the HTQ tracing orders determine the Masked Threshold values for the pulsed tones, irrespective of pre-rest or post-rest tracing positions. It would appear that the subject has set up, on the basis of his HTQ tracings, a mental yardstick, so to speak, which is carried over to the threshold tracing in the noise treatment. Therefore, differing absolute shifts in noise could be interpreted as being the result of a psychological phenomenon associated with the thresholds of audibility and tonality in quiet.

Differences in HTQs, projected as they are to the MTs and also to RTs, would appear to be the normal correlate from which psychological deafness could arise. The differences observed here likewise would help to explain variations in absolute threshold shifts in noise for pathological ears as well, with one exception. The exception refers to those cases of pure VIIIth nerve deafness, as in acoustic tumor, where the shift in noise for the affected ear is greater than in cochlear lesions. One of the authors (C. G.) has used a modified version of the Langenbeck test for a number of years and has found it effective for differentiating cochlear from retro-cochlear insults.

Continuous tones in noise appear to be different in the pre-rest and post-rest

tracing positions Therefore threshold shifts under noise for continuous tones cannot be interpreted in the same manner as has been suggested for pulsed tones With reference to the former, the recovery thresholds suggest an interpretation of physiological fatigue This last point will be discussed indirectly in a succeeding section

RT Treatment

In the results section of this study it was noted that post rest pulsed tone recovery thresholds were significantly more sensitive than pre rest continuous tone recovery thresholds However a similar finding did not obtain in the reverse order Again recovery for continuous tones appears to be poorer than recovery for pulsed tones when the former were preceded by threshold tracings in quiet In other words, ITQs traced immediately before the MT(C) tracings shifted the aforementioned thresholds in noise much greater than when the MT(C) tracings were preceded by one hour of rest In addition the recovery thresholds for the former were poorer than for the latter This finding did not obtain for the pulsed tones These results give rise to an observation pertaining to the cumulative effects of 6 minutes of tonal threshold tracings in quiet upon subseqent continuous tone recovery patterns There appears to be a physiological fatiguing effect associated with continuous tone threshold tracings

TTS Comparisons

It was pointed out that three of the four ITQ(C)s were significantly more acute than the corresponding RT(C)s However only one ITQ(P) was significantly different from the corresponding RT(P) As discussed previously, these findings would seem to suggest that noise had a more deleterious effect upon continuous tones than upon pulsed tones The result therefore suggests a physiological fatigue from the low level noise relative to the continuous tone tracings as contrasted to the psychological one postulated for the pulsed tones The fact that the RTs for the pulsed tones recovered to the ITQ levels in three of the four tracings appears to substantiate this postulation

Additional Research

In view of the above discussed order effects future research with *fixed* frequency Bekesy tracings could be directed toward investigating the effects of a pulsed tone on a succeeding pulsed tone of a continuous tone on a succeeding continuous tone, of a first tonal presentation at a higher or lower frequency on a second tone at the test frequency (with various combinations of tonal presentation described above) and of a low level noise stimulation on a succeeding continuous or pulsed tone

SUMMARY AND CONCLUSIONS

The present study was undertaken to investigate order effects on fixed frequency tracings at 4000 cps made with a Bekesy type automatic audio

meter. Threshold values were determined on 32 normal hearing adults from tracings made in quiet, in low level noise and in recovery following noise termination. The subjects were randomly assigned to four test orders to evaluate the effects of tonal presentation during the three experimental conditions.

With regard to the questions which were posed in the study, it was found that initial threshold tracings in quiet for pulsed tones were more acute when they succeeded rather than preceded initial threshold tracings in quiet for continuous tones. However, thresholds in quiet for continuous tones did not differ, irrespective of whether they preceded or succeeded the pulsed tone thresholds. Furthermore, there were no differences in threshold sensitivity between pulsed and continuous tones when the former preceded the latter. This finding substantiates Jerger's (10) diagnostic use of the pulsed/continuous tone fixed frequency tracing order, at least for 4000 cps. In the reverse order, however (continuous/pulsed), the pulsed threshold was significantly more acute than the continuous threshold. This finding of improved threshold sensitivity for pulsed tones when preceded by continuous tones was interpreted as being a manifestation of the two thresholds, e.g. the threshold of tonality and the threshold of audibility. Implications of the finding were discussed.

Order effects were also found to be associated with continuous and pulsed tone threshold tracings in the Masked Threshold treatment which were related to the pre rest and post rest tracing positions. Significant threshold differences were found, however, only when the pre rest continuous tones preceded the post rest pulsed tones. The direction of greater pulsed tone sensitivity was, therefore, similar to that which was found in the ITQ tracings. Pulsed tone MT values appear to be related to the corresponding ITQ values. The pulsed tone finding was interpreted to be another manifestation of a psychological phenomenon. This interpretation was not, however, applicable with reference to continuous tone threshold values. The observed change in continuous tone thresholds was interpreted as being the result of physiological factors.

Tracing order effects were also found to be operating in the Recovery Threshold treatments. Post rest pulsed tone Recovery Thresholds were significantly more sensitive than pre rest continuous tone Recovery Thresholds. In addition, recoveries for pulsed tones were better than recoveries for continuous tones when the continuous tones were immediately preceded by ITQ tracings. Briefly, the ITQs traced before MT(C) tracings shifted the aforementioned thresholds in noise to a greater degree than when MT(C) tracings were preceded by an hour rest period. In addition, the Recovery Thresholds for the former were poorer than for the latter. This finding did not obtain for the pulsed tones. Apparently 6 minutes of quiet threshold tracings preceding a continuous tonal tracing in noise predisposes the ear to cumulative fatigue effects.

When Initial Thresholds in Quiet were compared with their corresponding

Recovery Thresholds following low level noise stimulation significant differences were found in three out of four instances with continuous tones The RTs for continuous tones were significantly poorer than the corresponding ITQs With respect to the pulsed tones the ITQs differed from the RTs in only one tracing order This finding suggests a physiological fatigue factor relative to continuous tone tracings which is in contrast to the psychological factor postulated for pulsed tone threshold differences

Implications relative to the findings as well as directions for additional research were discussed

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DISTORTED SPEECH AND BINAURAL SPEECH RESYNTHESIS TESTS

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Monaural distorted speech and binaural speech resynthesis tests were used in detecting central auditory damage in 18 patients with intracranial expanding lesions. In the binaural speech resynthesis test the speech material first was divided acoustically by means of filters. One low frequency part was presented to one ear and one high frequency part to the other ear, after which the resynthesis mechanism was assessed binaurally. In the monaural test the speech was fed through a combination of these two filters simultaneously, after which the resynthesis ability of each ear was compared with the binaural discrimination scores. The monaural distorted speech test gave positive results, i.e. a discrimination loss was demonstrated for the contralateral ear only in patients with unilateral intracerebral temporal lobe lesions. The binaural speech resynthesis test gave negative results, i.e. a reduction in the ability to resynthesize speech was not demonstrated in any of the patients with expanding intracranial processes.

Since the end of the last century repeated attempts have been made to differentiate and diagnose hearing disturbances due to damage to the central auditory pathways and to their projection areas in the temporal lobe. Neither tuning fork tests nor pure tone audiometry, however, have yielded any characteristic patterns indicating disturbances of the central auditory system.

Tests of discrimination ability with speech audiometry can sometimes give an indication that a central disturbance exists. Speech audiometry in its present form, however, is not sufficiently sensitive to show less pronounced central auditory disturbances.

During the last decade the opinion has been put forward that even minor losses of function would be rendered perceptible if the speech audiometry applied was made more difficult. In this way increased demands would be placed on the central auditory pathways and on the capacity of the auditory centre to interpret the test material. Promising results have been achieved with various more difficult tests, especially the test in which the speech frequency range is reduced with filters (distorted speech) (Bocca *et al.* 1954–57). In cases of damage in the temporal region there has often been found a reduced ability to perceive frequency distorted speech in the ear contralateral to the lesion.

Considerable attention has also been attracted by the method introduced

by Matzker (1956–59) This is based on an observation by Fletcher (1929) that the brain is normally able to resynthesize speech which has been divided electro acoustically into two halves if one half is listened to by one ear and the other half is simultaneously listened to by the other ear

In 1957 and 1958 Matzker reported his results with normal subjects and with patients having different central disturbances He divided the speech electro acoustically into two channels and introduced frequency distortion in both channels by means of bandpass filters A low frequency range between 500 and 800 cps was left in one channel and a high frequency range between 1500 and 2400 cps in the other Later (1959) the high frequency range was changed to 1815 2500 cps

The low and the high channel allowed in each case an intelligibility of not more than 26 and 30 per cent respectively of a test material consisting of words of two and three syllables If however the low channel was listened to by one ear and the high channel simultaneously by the other ear healthy persons with normal hearing in the age group 20 60 years could understand practically the whole of the test material correctly The two speech fractions which separately were difficult to understand could thus be resynthesized *centrally to give a unitary speech perception with good intelligibility*

A disturbed resynthesis mechanism could under physiological conditions be demonstrated in children and old persons and moreover in a large number of different pathological conditions with probable cerebral lesions such as cerebral atrophy hypertonia multiple sclerosis cranial trauma and epilepsy Of principal interest however from the point of view of diagnosis were *brain tumours* Matzker demonstrated reduced ability to resynthesize *in 32 cases in a series of 38 intracranial expanding lesions of different kinds mainly tumours* Reduced ability to resynthesize was observed independently of the localization of the lesions the intracranial pressure *and the duration of the symptoms*

As a speech resynthesis test should have considerable diagnostic importance and perhaps *enable* us to improve our understanding of central auditory damage a method similar *to Matzker's* using Swedish word material has been worked out

A clinical evaluation of the distorted speech and the binaural speech resynthesis tests has been made on a series of patients with verified central damage (Linden 1960)

APPARATUS

Preliminary discrimination experiments with various test materials were made using band pass filters *of different* frequency ranges widths *and* steepness of cut off Two one third octave filters were eventually chosen one in the lower and one in the higher part of the speech fequency range With these filters it was possible to *carry out* a binaural resynthesis test according to the criteria laid down by Matzker as well as to investigate the monaural ability to comprehend distorted speech *according* to *Bocca et al*

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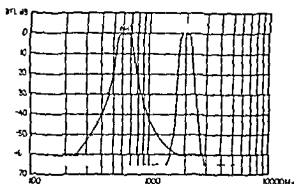


Fig. 1. Frequency curve of the speech audiometer with the low and high frequency filters connected. The higher filter consists of two one-third octave filters in series.

The band pass filters were connected to a speech audiometer system with good electro-acoustic properties. In the audiometer the speech could be divided into two channels, one carrying the low frequencies, the other the high ones. Separately each channel gave a low intelligibility of speech in discrimination tests, but if they were led simultaneously one to each ear the divided material could be centrally resynthesized to a unitary speech perception with good intelligibility.

The frequency curve of the speech audiometer with the two filters connected is seen in Fig. 1. The lower filter passes the band 560–715 cps measured 3 db below the level of the mid frequency 640 cps. The higher filter which actually consists of two one-third octave filters in series passes the band 1800–2200 cps with the midfrequency 2000 cps. By feeding speech through the combination of the same low and high filters monaurally it was possible to compare the discrimination score to that in the binaural resynthesis test.

WORD MATERIAL

In order to judge the suitability of different types of word material intelligibility tests were made through the filters with monosyllabic words, dissyllabic words of spondaic type, three-digit numbers and sentences. Of the word material investigated, spondees proved the most suitable as test material. By means of further intelligibility tests there were chosen from a very large word series a number of spondees with a low intelligibility within the lower and within the higher frequency range. At the same time it was endeavoured to choose spondees with fairly good intelligibility when the word material was presented through a combination of the two filters, whether the two channels were led simultaneously to one ear or one channel was led to one ear and the other channel simultaneously to the other ear. Of the original material of about 900 spondees there finally remained only 135 spondees which fulfilled these requirements for intelligibility. These were divided up into 9 lists of 15 words each, which were shown experimentally and statistically to be of equal difficulty both with and without filtering.

The word material was recorded on tape along with a calibration tone at a level corresponding to the average deflections of the test words on a VU meter. The words were presented every five seconds without a carrier phrase.

TESTING OF METHODS

The purely acoustic requirements for the distorted speech and the binaural speech resynthesis tests were investigated by means of different intelligibility tests. Discrimination tests were made on a total of 50 young persons with normal hearing.

The order of the lists was constantly varied in order to avoid the results being affected by familiarity and fatigue. The lists were presented with rising intensity according to the customary principles for speech audiometry. In order to eliminate differences in the individual hearing acuity the test material was presented at different sensation levels.

The discrimination tests were done in the following ways: (*a*) monaurally through the 640 cps filter, (*b*) monaurally through the 2000 cps filter, (*c*) monaurally through both filters at once (*monaural distorted speech test*), (*d*) binaurally through 640 cps filter to one ear and 2000 cps filter to the other ear (*binaural speech resynthesis test*).

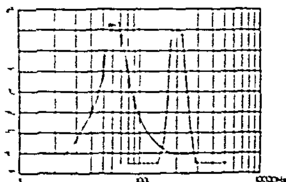
The results of the discrimination tests will be seen in Figs. 2–4 and Tables *1 3*. Through the 640 cps filter, the intelligibility was low at sensation levels of 30 and 40 db but rose with increasing intensity. For some lists intelligibility rose quite rapidly between 40 and 50 db. For the binaural speech resynthesis test therefore the sensation level should not exceed 40 db. If the intensity is raised above this level there is a risk that the main part of the information in the resynthesis test may be conveyed by the lower channel alone.

Through the 2000 cps filter the intelligibility of spondees was very low and

TABLE 1. *Discrimination tests monaurally through 640 cps filter.*

Ten spondee lists were presented at sensation levels of 30, 40, 50 and 60 db. 20 normal hearing subjects. M = means of per cent intelligibility. L = limits of variation in per cent. TM = total means. ML = means of limits of variation.

		1	2	3	4	5	6	7	8	9	TM	ML
30 db	M	5.8	7.5	4.5	6.7	8.9	8.5	4.5	8.0	7.1	6.7	± 2.2
	L	13.3	20.0	13.3	13.3	13.3	13.3	13.3	20.0	20.0	15.3	
40 db	M	9.3	14.7	11.7	11.7	19.0	15.0	9.0	16.0	17.0	14.0	± 3.5
	L	20.0	33.3	26.7	33.3	26.7	26.7	20.0	33.3	33.3	28.1	
50 db	M	29.3	29.0	25.0	26.3	39.7	31.7	26.0	30.3	38.3	30.7	± 5.1
	L	40.0	33.3	26.7	33.3	40.0	26.7	26.7	53.3	33.3	34.8	
60 db	M	50.3	43.3	37.0	39.7	55.0	46.0	40.0	48.7	54.0	46.0	± 6.0
	L	33.3	33.3	40.0	40.0	40.0	40.0	33.3	53.3	26.7	38.0	



... curve of the speech audiometer with the low and high frequency filters ... filter consists of two one third octave filters in series.

The band pass filters were connected to a speech audiometer system with good electro-acoustic properties. In the audiometer the speech could be divided into two channels, one carrying the low frequencies, the other the high ones. Separately each channel gave a low intelligibility of speech in discrimination tests, but if they were led simultaneously one to each ear the divided material could be centrally resynthesized to a unitary speech perception with good intelligibility.

The frequency curve of the speech audiometer with the two filters connected is seen in Fig. 1. The lower filter passes the band 560–715 cps, measured 3 db below the level of the mid frequency 640 cps. The higher filter, which actually consists of two one third octave filters in series, passes the band 1800–2200 cps with the midfrequency 2000 cps. By feeding speech through the combination of the same low and high filters monaurally it was possible to compare the discrimination score to that in the binaural resynthesis test.

WORD MATERIAL

In order to judge the suitability of different types of word material intelligibility tests were made through the filters with monosyllabic words, dissyllabic words of spondaic type, three digit numbers and sentences. Of the word material investigated, spondees proved the most suitable as test material. By means of further intelligibility tests there were chosen from a very large word series a number of spondees with a low intelligibility within the lower and within the higher frequency range. At the same time it was endeavoured to choose spondees with fairly good intelligibility when the word material was presented through a combination of the two filters, whether the two channels were led simultaneously to one ear or one channel was led to one ear and the other channel simultaneously to the other ear. Of the original material of about 900 spondees there finally remained only 135 spondees which fulfilled these requirements for intelligibility. These were divided up into 9 lists of 15 words each, which were shown experimentally and statistically to be of equal difficulty, both with and without filtering.

The word material was recorded on tape along with a calibration tone at a level corresponding to the average deflections of the test words on a VU meter. The words were presented every five seconds without a carrier phrase.

TESTING OF METHODS

The purely acoustic requirements for the distorted speech and the binaural speech resynthesis tests were investigated by means of different intelligibility tests. Discrimination tests were made on a total of 50 young persons with normal hearing.

The order of the lists was constantly varied in order to avoid the results being affected by familiarity and fatigue. The lists were presented with rising intensity according to the customary principles for speech audiometry. In order to eliminate differences in the individual hearing acuity the test material was presented at different sensation levels.

The discrimination tests were done in the following ways: (*a*) monaurally through the 640 cps filter, (*b*) monaurally through the 2000 cps filter, (*c*) monaurally through both filters at once (*monaural distorted speech test*), (*d*) binaurally through 640 cps filter to one ear and 2000 cps filter to the other ear (*binaural speech resynthesis test*).

The results of the discrimination tests will be seen in Figs. 2–4 and Tables 1–4. Through the 640 cps filter the intelligibility was low at sensation levels of 30 and 40 db but rose with increasing intensity. For some lists intelligibility rose quite rapidly between 40 and 50 db. For the binaural speech resynthesis test therefore the sensation level should not exceed 40 db. If the intensity is raised above this level there is a risk that the main part of the information in the resynthesis test may be conveyed by the lower channel alone.

Through the 2000 cps filter the intelligibility of spondees was very low and

TABLE 1. *Discrimination tests monaurally through 640 cps filter*

The spondee lists were presented at sensation levels of 30, 40, 50 and 60 db. 20 normal hearing subjects. M = means of per cent intelligibility. L = limits of variation in per cent. TM = total means. ML = means of limits of variation.

		1	2	3	4	5	6	7	8	9	TM	ML
30 db	M	5.8	7.5	4.5	6.7	8.9	8.5	4.5	8.0	7.1	6.7	± 2.2
	L	13.3	20.0	13.3	13.3	13.3	13.3	13.3	20.0	20.0	15.3	
40 db	M	9.3	14.7	11.7	11.7	19.0	15.0	9.0	16.0	17.0	14.0	± 3.5
	L	20.0	33.3	26.7	33.3	26.7	26.7	20.0	33.3	33.3	28.1	
50 db	M	29.3	29.0	[illegible]	26.3	38.7	31.7	26.0	30.3	38.3	30.7	± 5.1
	L	40.0	33.3	26.7	33.3	40.0	26.7	26.7	53.3	33.3	34.8	
60 db	M	50.3	43.3	37.0	39.7	55.0	46.0	40.0	48.7	54.0	46.0	± 6.0
	L	33.3	33.3	40.0	40.0	40.0	40.0	33.3	53.3	26.7	38.0	

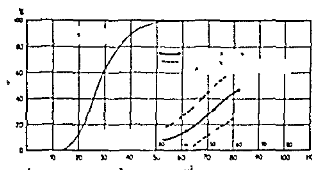


Fig. 2. Mean curve of intelligibility tests with spondee lists monaurally through 640 cps filter and mean curves of limits of variation. 20 normal subjects.

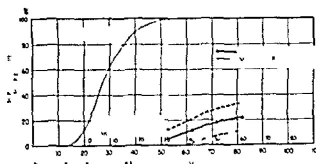


Fig. 3. Mean curve of intelligibility tests with spondee lists monaurally through 2000 cps filter and mean curves of limits of variation. 10 normal subjects.

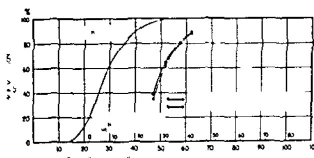


Fig. 4. Mean curves of monaural distorted speech and binaural speech resynthesis tests. 20 normal subjects.

it increased only a little with rising intensity. Normal subjects showed good ability to resynthesize centrally speech which had been divided into two channels and drastically restricted as to frequency. This resynthesis occurred at a level where the intelligibility for the low and the high frequency channel alone was poor (14.0 ± 3.[illegible] and 11.4 ± 3.5 %, respectively).

The corresponding investigation was made of intelligibility in monaural listening through the combination of the low and the high filter (monaural *distorted speech test*). The result was not significantly different. The hearing level for distorted speech in monaural listening was about 1.0 db lower than in binaural listening.

TABLE 2 *Discrimination tests monaurally through 2000 cps filter*

The spondee lists were presented at sensation levels of 30 40 50 and 60 db 10 normal hearing subjects M = means of per cent intelligibility L = limits of variation in per cent TM = total means ML means of limits of variation

		1	2	3	4	5	6	7	8	9	TM	ML
30 db	M	5.3	4.0	5.3	4.7	6.0	5.3	4.0	3.3	3.3	4.7	± 1.4
	L	13.3	6.7	13.3	13.3	13.3	13.3	13.3	6.7	6.7	11.3	
40 db	M	13.3	12.7	10.0	14.7	12.7	6.0	10.7	10.7	10.0	11.4	± 3.5
	L	13.3	13.3	20.0	26.7	13.3	13.3	26.7	26.7	6.7	18.0	
50 db	M	13.3	16.0	20.7	19.3	16.7	10.7	19.3	17.3	14.1	17.3	± 4.0
	L	20.0	26.7	26.7	13.3	20.0	13.3	20.0	20.0	33.3	21.3	
60 db	M	20.0	22.7	20.7	28.0	23.3	18.0	24.0	20.7	20.7	22.1	± 4.1
	L	20.0	20.0	26.7	33.3	20.0	20.0	33.3	13.3	13.3	22.0	

TABLE 3 *Comparison between intelligibility in distorted speech test and in binaural speech resynthesis test*

Four spondee lists were used for monaural listening through the combination of filters 640 cps and 2500 cps (distorted speech test) and four spondee lists for binaural listening with speech through 640 cps to one ear and simultaneously through 2000 cps filter to the other ear (binaural speech resynthesis test) The lists were presented at sensation levels of 25 30 35 and 40 db 20 normal hearing subjects —Results in per cent intelligibility

		25 db	30 db	35 db	40 db
Distorted speech test	Means	36.9±6.0	63.8±5.3	81.0±4.0	89.0±1.7
Binaural speech resynthesis test	Means	34.8±7.5	62.3±8.1	80.6±3.0	89.2±4.3

Clinical Testing of the Monaural Distorted Speech and the Binaural Speech Resynthesis Tests

A clinical test was made on patients with expanding intracranial lesions to investigate their ability to comprehend distorted speech and to resynthesize speech centrally

The Case Material

Speech audiometry examinations require good cooperation on the part of the patients A large number of cases of intracranial lesions must therefore be excluded in those cases where ordinary speech audiometry examinations could not be carried out owing to mental or general effects of disease or to the patient s youth Moreover, for technical reasons investigations with binaural speech resynthesis tests could not be carried out if a patient had too great a disparity between the thresholds of hearing in the two ears

Eighteen patients from the Neurosurgical Department of the Sahlgrenska

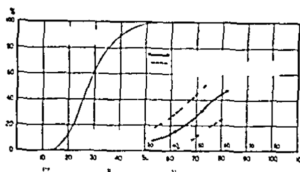


Fig. 2. Mean curve of intelligibility tests with spondee lists monaurally through 640 cps filter and mean curves of limits of variation. 20 normal subjects.

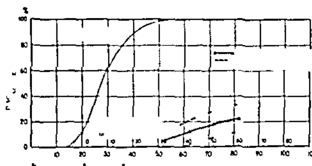


Fig. 3. Mean curve of intelligibility tests with spondee lists monaurally through 2000 cps filter and mean curves of limits of variation. 10 normal subjects.

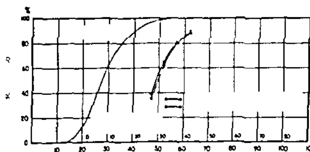


Fig. 4. Mean curves of monaural distorted speech and binaural speech resynthesis test. 0 normal subjects.

it increased only a little with rising intensity. Normal subjects showed good ability to resynthesize centrally speech which had been divided into two channels and drastically restricted as to frequency. This resynthesis occurred at a level where the intelligibility for the low and the high frequency channel alone was poor (14.0 ± 3.5 % and 11.4 ± 3.5 % respectively).

The corresponding investigation was made of intelligibility in monaural listening through the combination of the low and the high filter (monaural distorted speech test). The result was not significantly different. *The hearing* level for distorted speech in monaural listening was about 1.0 db lower than in binaural listening.

TABLE 5 *Patients with expansive intracranial affections outside the temporal region*

Patient No and sex	Patient Date of birth	Localization and kind of lesion	Diagnostic or therapeutic measures Date	Diagnostic or therapeutic measures Measure	Date of audiological examination	Distorted speech test Max intelligibility in per cent Right	Distorted speech test Max intelligibility in per cent Left	Binaural speech resynthesis test Max intelligibility in per cent
6 59	09 XX 48	Cerebellum astrocytoma	16 XI 16 XI	enc op	13 XI	60	60	57
7 58	11 XX 43	Ventriculus IV ependymoma	18 XII 19 XII 19 XII	a g enc op	18 XII	73	67	80
8 51	09 XX 20	Lobus frontalis sin aneurysma art venosa	12 IX 15 IX	a g enc	7 IX	80	87	82
9 58	05 XX 0[illegible]	Lobus frontalis sin astrocytoma	10 XII 18 XII	a g op	11 XII	80	93	83
10 51	04 XX 99	Lobus frontalis sin astrocytoma	23 VII 6 VIII 6 VIII	enc a g op	4 VIII	80	80	83
11 58	03 XX 00	Regio subfrontalis dx meningoma	11 XI 18 XI 8 XII	enc a g op	5 XII	60	67	67
12	04 XX 20	Fossa cranii media sin hygroma	4 II 5 II 9 II	enc a g op	7 II	80	80	80
13 59	07 XX 06	Regio parasagittalis dx meningoma	30 X 18 X	a g op	11 XI	83	87	92
14 53	10 XX 30	Corpus callosum affectio expansiva	29 XII 31 XII	a g enc	11 VIII	90	87	93
15 59	08 XX 91	Lobus parieto-occipitalis sin meningoma	7 X 16 X 6 I	enc a g autopsy	5 X	80	80	78
16	08 XX 03	Regio occipitalis sin metastasis (hypernephroma)	12 II 27 II	a g op	20 I	80	87	83
17	01 XX 98	Craniopharyngioma	28 XII	enc	14 VIII	80	80	78
18 51	10 XX 91	Adenoma hypophysis	12 X	op	23 IX	80	80	[illegible]0

logically reduced intelligibility for monaural distorted speech or a loss of intelligibility in the binaural resynthesis test could be observed, Békésy audiograms were taken to show possible recruitment. Owing to the effect of the tumour on mental processes in some cases Békésy audiograms could be taken since this examination calls for a pronounced effort

Table 4. *Patients with lesions in the temporal region*

…nt Date of birth	Localization and kind of lesion	Diagnostic or therapeutic measure: Date	Diagnostic or therapeutic measure: Measure	Date of audiological examination	Distorted speech test Max. intelligibility in per cent: Homolaterally	Distorted speech test Max. intelligibility in per cent: Contralaterally	Binural sp… resynthesis: Max. intelligibility in per cent	Filte… Righ…
6 XX 46	Lobus temporalis sin. glioma malign.	10 XI	op.	25 XI	87	*33*	*65*	640
9 XX 30	Regio fissurae Sylvii sin. astrocytoma	17 I 20 I 26 I	enc. a. g. exploration	18 I	93	*60*	80	2000
1 XX 09	Lobus temporalis sin. astrocytoma	24 XI	op.	6 XII	80	*33*	*47*	2000
1 XX 98	Regio fissurae Sylvii dx. astrocytoma	30 XII	op.	10 I	80	*20*	*47*	*2000*
1 XX 95	Regio temporalis sin. meningoma	17 XI 17 XII 19 XII	a. g. a. g. *op.*	16 XII 10 I	*53* *60*	*57* *73*	*54* *60*	2000

op. = operation, enc. = encephalography, a. g. = angiography

Hospital, Gothenburg, with roentgenologically or operatively verified expansive intracranial affections with different localizations were examined.

In accordance with the customary neurosurgical and neuroradiological nomenclature, not only tumours in the strict sense were counted as intracranial expanding lesions, but also other expanding lesions such as an arteriovenous aneurysm in the frontal lobe with pressure symptoms (case No. 8/59) and a hygroma in the middle cranial fossa (case No. 12/59). A large hypernephroma metastasis in the occipital bone grew extradurally but yielded pressure symptoms with rapidly progressing stasis papillae, on the occasion of the investigation 5 dioptria bilaterally (case No. 16/59).

The composition of the material will be seen from Tables 4 and 5. Table 4 presents 5 patients with damage in the temporal region and Table 5 presents 13 patients with expanding lesions outside the temporal region. Three patients were examined post-operatively only, the other patients pre-operatively.

General Audiological Examination

Apart from a complete ear, nose and throat examination and the customary otoneurological examination, each patient underwent an audiological examination with pure tone and speech audiometry.

If loss of hearing was revealed by pure tone audiometry or if a patho-

Results of Special Audiological Examination

The results of the investigation of the five patients with lesions in the temporal region will be seen in Table 4 In four cases reduction of the intelligibility with the monaural distorted speech test could be demonstrated in the contralateral ear (Cases Nos 1/58 2/59 3/58 and 4/59) Intelligibility in the homolateral ear on the other hand was normal A simultaneous reduction of intelligibility in the binaural resynthesis test also existed in three of these four cases (cases Nos 1/58 3/58 and 4/59) The intelligibility score for

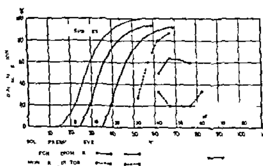


Fig 5 Case No 1 58 Boy 15 years old 10 IX 1958 exstirpation of a malignant glioma in left temporal lobe Speech audiometry 25 XI 1958

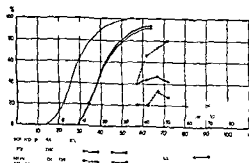


Fig 6 Case No 3 58 Male 49 years old 21 XI 1958 exstirpation of a large glioma in left temporal lobe Speech audiometry 6 XII 1958

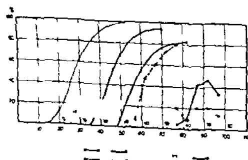


Fig 7 Case No 4 59 Male 60 years old 10 XII 1958 exstirpation of a glioma in right Sylvian fissure Speech audiometry 10 I 1959

of concentration on the part of the patient. Difference limens were normal in every case examined (8 patients)

Nine patients had practically normal hearing for tones within physiological limits. In 10 cases speech audiometry showed normal discrimination at a sensation level of 30 db In some cases the pure-tone and speech audiograms showed divergences from the norm but not to such an extent that this could be regarded as affecting the results in the binaural speech resynthesis test.

Special Audiological Examination: Monaural Distorted Speech and Binaural Speech Resynthesis Tests

Procedure of examination. Four of the nine spondee lists which had been prepared for the binaural speech resynthesis test were used, two to one ear and two to the other, through the combination of the low and high filters in order to assess the monaural intelligibility of distorted speech Five lists were used for judging the ability to resynthesize speech centrally.

Intelligibility curves were made by presenting the lists two and in some cases three times with rising intensity from a starting point 25–30 db above the patient's threshold for spondees The intensity was increased step by step by 5 db In this way it was possible in a reliable way to attain the sound level at which optimal intelligibility existed both for the monaural distorted speech test and for the binaural speech resynthesis test

If there was uniform hearing in both ears the low-frequency filtered speech passed to the left ear and the high-frequency range to the right ear as a matter of routine If, however, the hearing, judged by the pure-tone audiogram, *was better in the right ear for the low frequencies and/or better in the left ear for the high frequencies*, the low frequency range was applied *to the right ear and the high-frequency range to the left ear* In this way both frequency ranges could be employed under the most favourable conditions for the patient in question

Evaluation of the monaural distorted speech and the binaural speech resynthesis tests For normal subjects the lower limit for intelligibility was approximately 80 per cent, which means that 12 test words our of 15 were correctly understood The normal limits of variation, however, yielded in occasional cases and with some lists and intelligibility of only 11 correctly understood words per list Therefore no definite pathological significance was assigned to a score of 73 per cent intelligibility if it occurred as an isolated phenomenon with a single list

Primary importance in the evaluation of the binaural speech resynthesis test has, however, been assigned to the comparison between intelligibility scores achieved in this test and then in the monaural distorted speech test *Unless the intelligibility score in the binaural speech resynthesis test is definitely lower, the test cannot be said to be positive*

Results of Special Audiological Examination

The results of the investigation of the five patients with lesions in the temporal region will be seen in Table 4. In four cases reduction of the intelligibility with the monaural distorted speech test could be demonstrated in the contralateral ear (Cases Nos. 1/58, 2/59, 3/58 and 4/59). Intelligibility in the homolateral ear on the other hand was normal. A simultaneous reduction of intelligibility in the binaural resynthesis test also existed in three of these four cases (cases Nos. 1/58, 3/58 and 4/59). The intelligibility score for

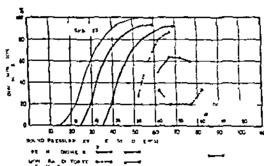


Fig. 5. Case No. 1/58. Boy, 15 years old. 10 IX 1958 exstirpation of a malignant glioma in left temporal lobe. Speech audiometry 25 XI 1958.

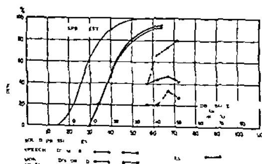


Fig. 6. Case No. 3/58. Male, 49 years old. 21 XI 1958 exstirpation of a large glioma in left temporal lobe. Speech audiometry 6 XII 1958.

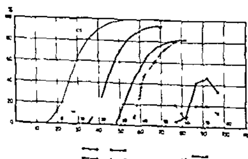


Fig. 7. Case No. 4/59. Male, 60 years old. 10 XII 1958 exstirpation of a glioma in right Sylvian fissure. Speech audiometry 10 I 1959.

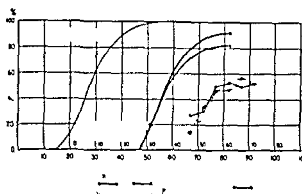


Fig. 8. Case No. 5/58. Female, 63 years old. 19.XII.1958 extirpation of a meningioma in the left temporal region. Speech audiometry 16.XII.1958.

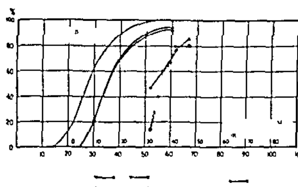


Fig. 9. Case No. 10/59. Male, 60 years. 11.VIII.1959 extirpation of a glioma [illegible] in the left frontal lobe. Speech audiometry 4.VIII.1959.

the binaural resynthesis test in these cases lay between the intelligibility scores for the two ears in the monaural distorted speech test (Figs. 5–7).

The fifth patient with damage in the temporal region (case No. 5/58) had a large meningoma above the left temporal lobe and presented, in addition to a certain decline in mental level, a slight expressive aphasia. The intelligibility score for monaural distorted speech was reduced in both ears to approximately the same extent (Fig. 8). The intelligibility score in the binaural speech resynthesis test was reduced by the same amount, hence the test result must be regarded as negative.

The results of the investigation with the binaural speech resynthesis test on the thirteen patients with expanding intracranial lesions localized outside the temporal region will be seen in Table 5. In ten patients normal intelligibility could be demonstrated in the binaural speech resynthesis test. Typical examples of negative results from this test are shown in Figs. 9–12. There we find ordinary speech audiograms and intelligibility curves for monaural distorted speech and for the binaural speech resynthesis test in four patients with expanding intracranial lesions in different sites (cases Nos. 10/59, 12/59, 13/59 and 14/59). The intelligibility for monaural distorted speech is the same in both ears, and the curves for this and for the binaural speech resynthesis test run parallel.

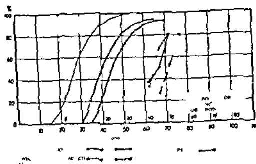


Fig. 10. Case No. 12/59. Male, 39 years old. A hygroma in the left middle cranial fossa was emptied on XII 1959. Speech audiometry 7 XII 1959.

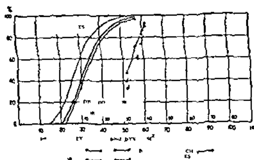


Fig. 11. Case No. 13/59. Male, 53 years old. 18 XI 1959 extirpation of a parasagittal meningioma in the right parietal region. Speech audiometry 14 XI 1959.

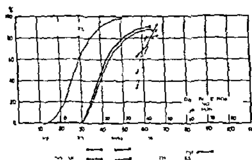


Fig. 1[illegible]. Case No. 14/59. Male, 28 years old. Inoperable tumour in corpus callosum. Angiography 19 VII 1959. Speech audiometry 11 VIII 1959.

Only two patients had significantly lower values than normal subjects in the binaural speech resynthesis test (cases Nos. [illegible]/59 and 11/58). Both these patients, however, had at the same time a bilateral reduction of intelligibility for monaural distorted speech. Reduction of intelligibility with the binaural speech resynthesis test was in no case percentually more pronounced than the bilateral reduction of intelligibility for monaural distorted speech. Again the intelligibility curves for monaural distorted speech for the two

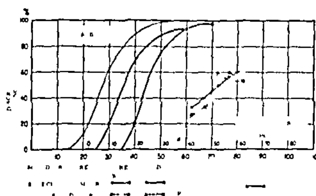


Fig. 13. Case No. 6/59. Girl 11 years old. 16 XI 1959 exstirpation of an astrocytoma in cerebellum. Speech audiometry 13 XI 1959.

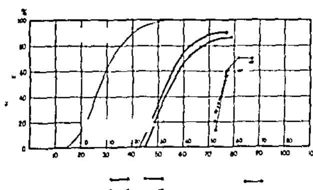


Fig. 14. Case No. 11/58. Female 58 years old. 8 XII 1959 exstirpation of a meningioma in the anterior cranial fossa. Speech audiometry 5 XII 1959.

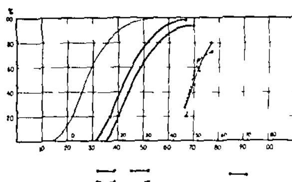


Fig. 15. Case No. 7/58. Boy 10 years old. 19 XII 1958 exstirpation of an ependymoma in the fourth ventricle. Speech audiometry 18 XII 1958.

ears separately and for the binaural speech resynthesis test ran practically parallel (Figs. 13 and 14).

One of these patients (case No. 6/59) was an 11 year old girl with a tumour in the posterior cranial fossa and slightly affected general condition. In the second case the patient was a 58 year old woman who had a large subfrontal meningioma and decline in mental level (case No. 11/58).

Slightly reduced intelligibility in both ears for monaural distorted speech

without simultaneous reduction of intelligibility in the binaural speech resynthesis test could be shown in case No 7/58 (Fig 15) In spite of a certain general effect of the tumour which was located in the fourth ventricle, the binaural speech resynthesis score was not reduced

The series of patients with expanding intracranial lesions was sufficiently large to permit of an evaluation of the clinical value of the binaural speech resynthesis test

Significantly low values for the intelligibility with the binaural speech resynthesis test could be shown in a total of 6 out of 18 cases These 6 cases however had at the same time a unilateral or bilateral reduction of the intelligibility for monaural distorted speech *A positive result of the binaural speech resynthesis test was not obtained in any case in the sense that the intelligibility in this test was reduced to a lower value than that for the monaural distorted speech test*

DISCUSSION

In patients with unilateral temporal lobe tumours Bocca *et al* (1955) found asymmetrical perceptive ability with the aid of speech made difficult to understand by frequency distortion

In the investigation now carried out in four cases out of five with unilateral temporal lobe damage a decline of intelligibility in the monaural distorted speech test could be shown in the contralateral ear In the fifth case—a meningoma—the temporal lobe was compressed but not destroyed and was not removed in the operation Nor was any asymmetrical reduction of discrimination found post operatively in this case The present material of temporal lobe damage is in itself small but the results of the monaural distorted speech test for these patients show good agreement with the results obtained by Bocca *et al*

The binaural resynthesis tests with speech reported by Matzker appeared to offer good opportunities for a very general assessment of the central auditory function Matzker stated that hearing impairment of central *origin* with difficulties in speech resynthesis had been shown in 32 out of 38 patients with brain tumours of *various kinds* and sizes and *independently of the localization* of the tumour

Matzker's results with *patients* with brain tumours could not however be confirmed on *investigation* with the Swedish binaural speech resynthesis test carried out on a series of patients with expanding intracranial lesions Several factors may contribute to explain the differences

From an audiological point of view the binaural resynthesis test as developed by Matzker has *some uncertain elements*

1 The intelligibility for frequency distorted speech was judged in both ears simultaneously

2 The test material was listened to at only one level This level was the level at which a number of questions after filtering through the band pass filters achieved maximum intelligibility

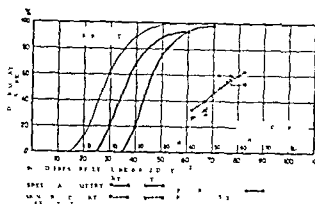


Fig 13 Case No 6/59 Girl, 11 years old 16 XI 1959 exstirpation of an astrocytoma in cerebellum Speech audiometry 13 XI 1959

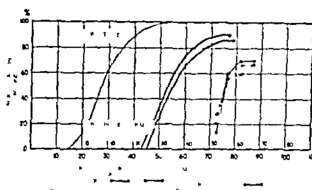


Fig 14 Case No 11/58 Female, 58 years old 8 XII 1959 exstirpation of a meningoma in the anterior cranial fossa Speech audiometry 5 XII 1959

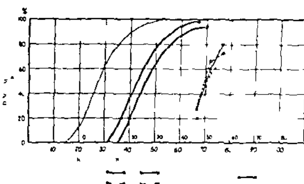


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From an audiological point of view the binaural resynthesis test as developed by Matzker has some uncertain elements

1 The intelligibility for frequency distorted speech was judged in both ears simultaneously

2 The test material was listened to at only one level This level was the level at which a number of questions after filtering through the band pass filters achieved maximum intelligibility

3 The comparison between the central resynthesis ability for speech and the intelligibility for filtered speech was carried out with the same word material. The test material was listened to in unchanged form both in the binaural speech resynthesis test and in the intelligibility test with frequency distorted speech.

4 Finally there was a potential risk of subjective evaluation of the resynthesis test by reason of the fact that a number of words were accepted as correctly understood if they only had the same vowel pattern as the actual test words. The evaluation in doubtful cases depended in the last resort on a subjective evaluation by the investigator based on his usage and experience of the test.

In view of this a number of important modifications were made when devising the Swedish binaural speech resynthesis test. The underlying principles of the resynthesis test however were not affected.

1 A monaural reduction of intelligibility for filtered speech should reasonably be supposed to involve a simultaneous reduction of the ability of the auditory centre to utilize the information from the same ear in a resynthesis test. It was therefore considered extremely important that not only ordinary speech audiometry investigation should be undertaken but that intelligibility for filtered speech should be examined in each ear separately.

2 The intelligibility curve for spondees can in spite of marked frequency distortion be steep. An evaluation of the intelligibility in a resynthesis test with spondees at only one level may therefore be difficult. The investigation may easily take place at a level at which the intelligibility curve is steepest. A difference of only a few db can give a percentually very large difference in intelligibility. The optimal resynthesization ability for speech was therefore evaluated by doing the intelligibility test at different levels by which means a complete intelligibility curve was obtained.

3 Different spondee lists were used in the binaural speech resynthesis test and in the intelligibility test with frequency distorted speech only. Memory which is differently developed in different individuals could then not affect the outcome of the investigation.

4 In order to be able to evaluate the intelligibility objectively only those tests words which were correctly understood were accepted in scoring the test.

These test requirements important from an audiological point of view were mainly intended to make it possible to investigate whether a reduction of intelligibility in the binaural speech resynthesis test could be caused by central resynthesis difficulties with a monaurally normal ability to comprehend filtered speech or only expressed a monaural or binaural reduction of intelligibility for difficult speech. In addition increased certainty was gained in the technical execution of the binaural speech resynthesis test and increased objectivity in the evaluation of the results.

The binaural speech resynthesis test with Swedish word material had thus been formulated from the acoustic audiological and technical points of view in such a way that the central resynthesization ability could be properly evalu

ated The pathological material had been so selected that other factors which might render difficult the evaluation of the results were excluded Patients with general mental effects from the basic disease, patients who were too young and patients who had peripheral hearing impairments with reduction of discrimination even with ordinary speech audiogram were not included in the clinical testing of the resynthesis test

When these test requirements *were applied to the investigation technique and these criteria to the choice of patients there was in no case a positive outcome of the binaural speech resynthesis test in the sense that the intelligibility in the resynthesis test was reduced to a lower value than the intelligibility in the monaural distorted speech test in either ear*

Reduction of intelligibility in the binaural speech resynthesis test could be observed with bilateral reduction of capacity to understand filtered speech in conditions of slight decline of mental level The ability to resynthesize speech was in these cases reduced to the same percentual value as the intelligibility with filtered speech In these cases the reduced intelligibility in the resynthesis test may be regarded rather as a consequence of a generally reduced intelligibility for filtered speech in both ears than as a consequence of reduced ability to resynthesize centrally

Reduction of intelligibility in the resynthesis test was observed moreover with unilateral reduction of intelligibility for filtered speech that is to say in patients with unilateral temporal lobe damage As these patients probably found extreme difficulty in the resynthesis test also in *apprehending the* information defective as a result of frequency distortion which *was led to* the contralateral ear the decline of intelligibility in the resynthesis *test can* be quite satisfactorily explained in these cases On the other *hand the central* coordination of the binaural auditory impulses was so far as could be judged intact as the intelligibility in the resynthesis test *was higher than the* corresponding intelligibility at the same level with *monaural* listening to the test material both in the low frequency and in the high frequency channel

Thus *in no case* has any evidence been shown that the ability to resynthesize speech is *generally disturbed* in expanding intracranial lesions independently of *localization* The experiences *gained* from the binaural speech resynthesis test with Swedish word material diverged markedly *from the* results obtained by *Matzker* with his binaural speech resynthesis test *The results which have been obtained in the present work on a selected pathological series show clearly that the hopes which had been attached to the binaural speech resynthesis test have not been realized We have therefore considered that in the present conditions there is no case for incorporating the binaural speech resynthesis test with other audiological routine methods*

ZUSAMMENFASSUNG

Monaurale Sprachaudiometrie mit Frequenzdistortion und binaurale Gehörsynthesetest wurden zum Nachweisen von zentralen Gehörschaden bei 18 Patienten mit expansiver intrakranieller Affektion angewandt

Bei binauralem Gehörsynthesetest wurde die Sprache akustisch in ein Tiefpassband und ein Hochpassband geteilt und je einem Ohr zugeleitet, wobei man gleichzeitig mit beiden Ohren hörte, um die Sprache zu synthetisieren.

Beim monauralen Test wurde die Sprache durch eine Kombination der beiden Passbandssysteme jeweils nur zu einem Ohr geleitet, um nachher das Synthesevermögen der beiden einzelnen Ohren mit dem Resultat des binauralen Tests zu vergleichen.

Der monaurale Sprachaudiometrietest mit Frequenzdistortion erweist sich als positiv nur bei *einseitigem intrazerebralem Temporallobschaden* durch eine *Herabsetzung der Diskrimination im kontralateralen Ohr*.

Der binaurale Gehörsynthesetest zeigte sich als negativ, da eine Herabsetzung des zentralen Synthesevermögens der Sprache in keinem Fall von expansiver intrakranieller Affektion nachgewiesen werden konnte.

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STUDIES ON EXPERIMENTAL ALLERGIC (ISOIMMUNE) LABYRINTHITIS IN GUINEA PIGS

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By injection of guinea pig cochlea emulsified with Freund s adjuvant, it was possible to induce in the majority of guinea pigs the acoustical and histological disturbances which were interpreted as an isoimmunization to cochlea tissue, although the detection of anticochlea antibody failed No positive reaction occurred when adjuvant alone was injected The main histological changes were found in the spiral ganglion and stria vascularis In some animals hemorrhage in the scala tympani and disintegration of the organ of Corti were observed These changes generally corresponded to the acoustical threshold shifts Thus there may be possibilities that the inner ear disease of one ear could affect the opposite ear as the result of an autoimmune reaction

INTRODUCTION

The concept of autoimmune (or autoallergic) disease includes conditions which are due to the pathogenic effects of antibodies produced by an individual against components of his own tissues (Cavelti 1955)

Since the first recognition of a human autoimmune disease was made in 1904 by Donath and Landsteiner following diseases are considered to be caused by this autoimmune or autoallergic reaction Masugi nephritis Hashimoto thyroiditis ophthalmia sympathica phacoanaphylactic endophthalmitis some kind of multiple sclerosis the encephalitis following rabies vaccination aspermatogenesis and lupus erythematosus

An autoimmune response might occur according to Ziff (1961) as a result from one of three possible mechanisms 1) Excessive amounts of normal tissue constituents are liberated from tissue store with the result that a normal immune mechanism is stimulated to synthesize autoantibody There is as pointed out by Medawar (1956 1957) a group of substances which are presumably potentially antigenic for the individual but are anatomically and physiologically isolated from the reticuloendothelial system and therefore do not ordinarily produce autoantibodies An autoimmuniza

tion results from a breakdown of anatomic isolation by trauma or infection Included in this category are nervous tissue, lens protein, spermatozoal antigen and thyroglobulin. An isoimmune response to all these tissues has been produced by active immunization; 2) Altered tissue constituents are liberated from tissue stores and these stimulate a normal immune mechanism to synthesize autoantibody. Lawrence (1959) has suggested that specific environmental factors, such as infection, intoxication or trauma, may modify normal body constituents so that they become antigenic and lead to the formation of *antibodies which subsequently may attack the unmodified or native antigen* by cross reaction; 3) The amount and character of tissue constituents liberated from tissue sources are normal, but the host response to these substances *is abnormal with the result that autoantibody is produced This idea is* derived from the hypothesis of Burnet & Fenner (1949) that the major immunologic adjustments in which the organism learns to recognize "self" from "not self" take place in embryonic life.

On the other hand, a few authors recently assumed from their clinical experiences that the autoimmune reaction in the cochlea may be responsible for some of the inner ear deafness of unknown etiology. Lehnhardt (1958) reported cases of bilateral sudden deafness and proposed the etiological hypothesis that the degeneration in the organ of Corti resulted in producing anti cochlea antibody with which another organ of Corti reacted as the antigen in the individual body. Kikuchi (1959) under the title "On the Sympathetic Otitis" reported several cases in which hearing in the opposite ear had been markedly influenced by the operation of the other ear

We also considered *the inner ear to be eligible* as a target organ *of autoimmune* reaction on the basis of the following reasons 1) Experimental allergic encephalomyelitis (Rivers *et al*, 1933, Freund *et al*, 1947, Kabat *et al*, *1947; Kopeloff & Kopeloff, 1947, Morgan, 1947, Lipton et al*, *1953)* is a well known autoimmune disease produced by sensitization to homo- and autologous brain tissue Ophthalmia sympathica is also considered to be one of the autoimmune diseases Embryologically, the cochlea is analogous to these organs 2) In general, autoimmune diseases are induced in such organs of which constituents are separated from general circulation, as described above The inner ear is also considered to have a barrier to blood circulation 3) These organs develop relatively later in embryonal life 4) The disturbances of both ears of bilateral inner ear deafness sometimes follow the same processes as pointed out by Lehnhardt (1958)

As far as reviewed papers are concerned, Beickert (1961) was the first to publish the experimental data concerning autoimmune reaction in the cochlea, and he used serological and nondecalcified histological methods The present authors made a model experiment of autoimmune disease of the cochlea in the form of iso immunization of the guinea pig examined by means of auditory, immunological and routine histological methods The present report will make a contribution to this problem because our methods and data were somewhat different from those of *Beickert*

MATERIAL AND METHOD

As experimental animals 41 healthy male guinea pigs weighing 250 to 300 gr were used. These were divided into A and B group according to the kind of adjuvant injected. Five animals in each group and 10 untreated normal guinea pigs were used as control. The experiment was scheduled as follows: Sensitization with antigen accompanied with weekly hearing tests, intravital fixation immediately after the extraction of the blood and the resection of a piece of the intestine canal for immunological tests.

Preparation of antigens injected

The tissue emulsion used for sensitization was prepared under sterile conditions as follows: immediately after intravital infusion with physiologic saline solution, cochleas, brain and kidney of each guinea pig were resected. The bony wall of the cochlea was removed as much as possible under binocular microscope. Ordinarily, the content of 20 cochleas including inner ear fluid was harvested and suspended in 1 ml of saline in a special small homogenizer, and was stored in refrigerator at −20°C. A mixture containing 2 mg heat killed M. tuberculosis, 2 ml paraffin oil and 1 ml Arlacel A (Atlas Powder Co.) was made as Freund's adjuvant, and was homogenized with 1 ml suspension of cochleas. This antigen was used for sensitization of 21 guinea pigs of A group. Ten guinea pigs of B group were inoculated with the mixture of 3 ml Difco's *Bacto adjuvant complete* (Difco Lab.) and 1 ml suspension of cochleas. The control animals of both A and B group were injected with the respective adjuvant only exclusive of cochlea. There is a slight difference of constituent and character between our own and Difco's adjuvant as mentioned below.

Injection of animals

In general, each guinea pig was injected with 0.4 ml of the antigen once a week for 5 to 8 weeks at several sites in the abdominal wall intracutaneously. However, some animals of A group were given intramuscular injections or injections with interval period as a booster injection. The detailed sensitization schedule of each animal is illustrated in Fig. 1.

Audiometric test

The hearing ability of the guinea pigs was measured once a week by means of the quantitative Preyer reflex. Both click tones of 4 000 and 8 000 cps generated from an oscillator were given through amplifier, 5 dB step attenuator and Hi Fi speaker. The intensity of tone given to guinea pigs was measured by the attenuator scale under the correction of sound level meter. All the instruments and animal's head were kept at a constant position throughout the experiment.

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In general each guinea pig was injected with 0 4 ml of the antigen once a week for 5 to 8 weeks at several sites in the abdominal wall intracutaneously However some animals of A group were given intramuscular injections or injections with interval period as a booster injection The detailed sensitization schedule of each animal is *illustrated in* Fig 1

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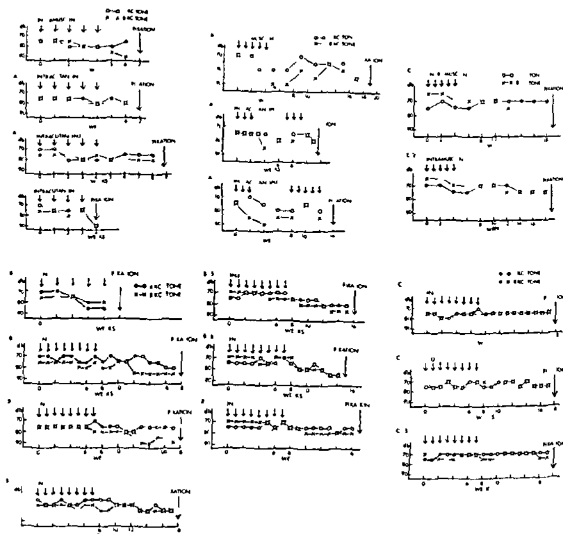


Fig. 1 illustrates the auditory threshold shifts measured by means of quantitative Preyer reflex and also indicates the injection times with arrows. Guinea pigs A 1 to A 7 belong to A group which was injected with emulsion of cochlea containing our own made adjuvant. C 1 and C 2 are the control animals of A group. Guinea pigs B 1 to B 7 belong to B group which was injected with Difco's adjuvant. C 1 to C 3 are the control animals of B group. Over 15 db threshold shifts for either 1 kc or 8 kc/cps. tone were regarded as the significant fluctuation of hearing.

Histological method

Fixation was made by aortic perfusion with Wittmaack's fixative immediately preceded by isotonic saline perfusion under light ether anesthesia. Then a specimen of the temporal bone was decalcified and embedded in celloidin. The serial sections were stained with hematoxylin-eosin. The brains and kidneys of the animals were also histologically examined.

Immunological tests

The test antigens used in immunological tests were prepared by low speed supernate procedure reported by Adler (1955). Protein content in the supernate of 10 cochleas emulsion in 10 ml saline solution was estimated from



FIG 2 Guinea pig A 6, right ear Cloudy swelling of the outer hair cells and Deiter cells, and nuclear pycnosis of the outer hair cells The 3rd turn 400

FIG 3 Guinea pig A 7, right ear (a) Atrophy of the stria vascularis in the 2nd and 3rd turn and precipitates in the scala vestibuli 50 × (b) Higher magnification of (a) Note the disappearance of the outer hair cells, shrinkage of the inner hair cells and extremely diminished mesothelial cells 400 × (c) High power view of the spiral ganglion in the 3rd turn of (a) The ganglion cells under degeneration and destruction were indicated with arrows 400 ×

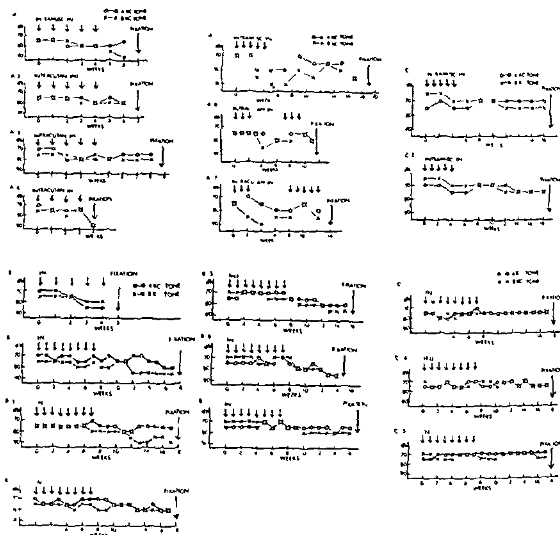


FIG. 1 illustrates the auditory threshold shifts measured by means of quantitative Preyer reflex and also indicates the injection times with arrows. Guinea pigs A 1 to A 7 belong to A group which was injected with emulsion of cochlea containing our own made adjuvant. C 1 and C 2 are the control animals of A group. Guinea pigs B 1 to B 7 belong to B group which was injected with Difco's adjuvant. C 1 to C 3 are the control animals of B group. Over 15 db threshold shifts for either 4 kc or 8 kc cps tone were regarded as the significant fluctuation of hearing.

Histological method

Fixation was made by aortic perfusion with Wittmaack's fixative immediately preceded by isotonic saline perfusion under light ether anesthesia. Then, a specimen of the temporal bone was decalcified and embedded in celloidin. The serial sections were stained with hematoxylin eosin. The brains and kidneys of the animals were also histologically examined.

Immunological tests

The test antigens used in immunological tests were prepared by low speed supernate procedure reported by Adler (1955). Protein content in the supernate of 10 cochleas emulsion in 10 ml saline solution was estimated from

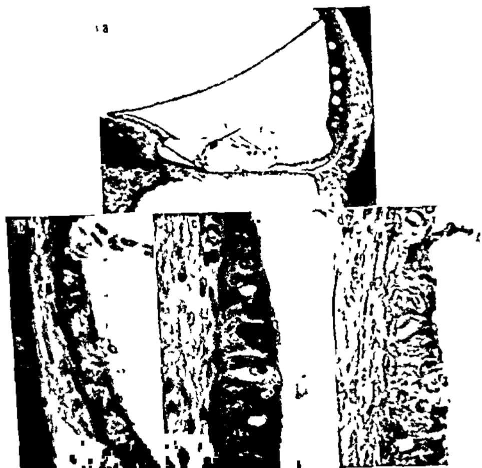


Fig 5 Pathological findings of the stria vascularis (a) Guinea pig A 2 right ear Dilated blood vessels of the stria vascularis in the 2nd turn 100 (b) Guinea pig A 6 right ear Degeneration of the stria with exudate and cell wandering in the endolymphatic space of the 3rd turn 400 (c) Guinea pig A 4 right ear Globular formation on the surface and space formation in the stria with slight degeneration 400 (d) Guinea pig A 1 left ear Localized edema of the stria of the 1st turn 400

cutaneous anaphylaxis (Ovary 1953 1958) Three hours after the intracutaneous injection of test serum at the site of healthy guinea pig s abdominal wall a mixture of 0 5 ml undiluted test antigen and 0 5 ml 0 5 per cent Evans Blue solution was intravenously injected After an hour, a blue spot might be observed on the internal side of the skin at the site of the former injection if the antigen reacts with the corresponding antibody 3) Schultz Dale test The 5 cm long fragments of ileum were resected from sensitized and control animals immediately before intravital fixation The movement of the ileum kept in 37°C Tyrode solution was recorded in order to observe the contraction evoked by antigen antibody reaction 4) Skin test The test antigens described above were intracutaneously injected into the sensitized and

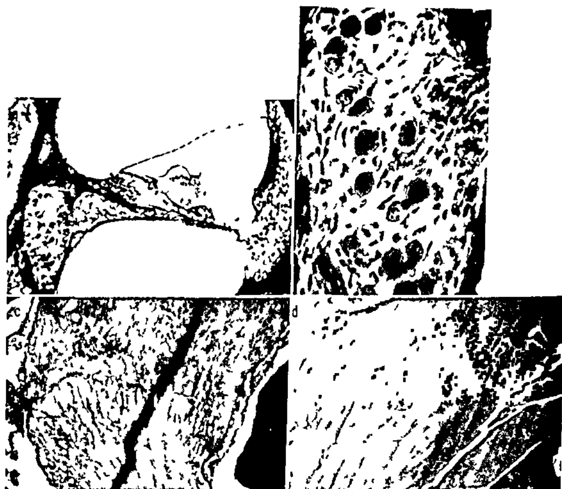


Fig. 4. Guinea pig B 1, right ear. The lesion localized in a half of the 2nd turn of the cochlea. (a) Cell debris under the atrophied tectorial membrane, degeneration of the organ of Corti and the reduced number of spiral ganglion cells were found. The organ of Corti was being replaced by connective tissue. Some cellular infiltration was found in the mesothelial cells. 80 ×. (b) Higher magnification of the spiral ganglion. The ganglion cells were in degeneration: swelling, disintegration and diminishing with mild infiltration of fibroblasts and monocytes. 300 ×. (c) The eighth nerve of the same cochlea. Note space formation in the nerve fibers. 50 ×. (d) The eighth nerve of a normal guinea pig. 50 ×.

107.5 to 120 μg N per ml by Kingsbury's method. The same procedures were also used to make the control test antigens from 1 per cent (100 mg wet weight in 10 ml cold saline) homogenates of brain and kidney, of which supernatants were estimated each 150 to 250 μg N per ml. The immunological tests used were as follows: 1) Boyden's tanned cell hemagglutination test (Boyden, 1951; Stavitsky, 1954). The procedures were performed by Stavitsky's method with slight modifications, *i.e.* 1/40 000 dilution of tannic acid and 1/10 dilution of test antigens containing 10.7 to 25 μg N per ml were used. To serially *diluted test serum was added the suspension of the* tanned sheep red cells which were coated with test antigen. If antigen-antibody complex was produced, hemagglutination is visible. 2) Ovary's passive

TABLE 1 *Effects of Injections of Guinea Pigs with Emulsions of Isologous Cochleas Containing Adjuvants*

Guinea pig No	Side	Over 15 db elevated threshold shift of Preyer reflex	Organ of Corti	Stria vascularis	Spir ggl cells	VIIIth nerve fiber	Perilymph and endolymph: Bleeding	Hydrops	Nubecula	Anti cochl antibody
A 1	r	−	−	+	+	−	−	−	−	−
	l		+	+	−	−		−	−	
A 2	r		−	+	−	−	−	−	+	−
	l		+	+	−		−	−	+	
A 3	r			+	+	−		−	+	−
	l		−	−	−	−	−	−		
A 4	r	+	−	+	+	−	−	+	−	−
	l		−	+	−	−	−	−	−	
A 5	r	+		−		−	+	−	−	
	l		−			−	+	−		
A 6	r		+	+	−		−	−	−	−
	l		−	+	+	−		−		
A 7	r		+	+	+		−		−	−
	l			+	−			−	−	
B 1	r			−	+	+	−	−	−	−
	l				+				+	
B 2	r			+	+		−	−	−	−
	l		−		+		−		−	
B 3	r					−	−	−	−	−
	l			−		−	−	−	−	
B 4	r		−		−	−	−	−	−	−
	l		−		−			−		
B 5	r						−	−		−
	l					−	−	−	−	
B 6	r						−	−		−
	l				+	−	−	−	−	
B 7	r				−	−	−	−	−	−
	l		−	−	−	−	−	−	−	
Total	28	8 14	5 28	15 28	15 28	1 28	3/	1	7/	0

animals remained in elevation until their *sacrifices* *The thresholds of 2* guinea pigs A 6 and A 7 *which received booster* injections with interval period of 5 to 6 weeks *seemed to increase in accordance* with the injections

The threshold shifts of *each control* animal were *within 10 dB as illustrated*

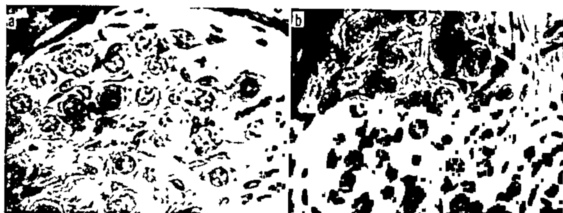


Fig. 6. Pathological changes of the spiral ganglion cells. (a) Guinea pig B 6, left ear. Nuclear pycnosis, swelling and disintegration of the ganglion cells in the 1st turn were indicated with arrows. 400 ×. (b) Guinea pig B 5, left ear. Nuclear pycnosis of the ganglion cells in the 1st turn. 400 ×.

control animals at the site of dorsal skin 24 hours previous to their sacrifice to prevent from desensitization. The animals of A-group and its controls received only first and second tests, while those of B-group and its controls were given all four tests.

RESULTS

Among 41 guinea pigs inoculated, 9 of A-group including 2 controls and 10 of B-group including 3 controls were able to receive all the tests described above. Seventeen guinea pigs of A-group including 3 controls and 5 of B-group including 2 controls had to be discarded due to their unpredicted deaths or a few failures of intravital fixation. The general conditions of each animal injected became worse in consequence of the injections, especially the toxic effect was so much stronger in the animals of A group that mortality was larger and the skin of the injected site fell into ulceration, while the effect was milder in B group.

Audiological data

The fluctuation of the thresholds for either 4,000 and 8,000 cps. tones in individual animals is illustrated in Fig. 1 with indications of inoculations. Though Gerstner (1942) measured ±3 dB threshold shifts of normal guinea pigs by means of the quantitative Preyer reflex spaced a week apart, the authors decided that the shift over 15 dB for either 4,000 or 8,000 cps. tone was regarded as a significant fluctuation of hearing ability because the maximum shift of normal guinea pigs measured by us was 10 dB. Eight of 14 guinea pigs inoculated with cochlea showed impaired hearing. Of interest was the fact that the once elevated thresholds of 2 guinea pigs, A 5 and A 7 again lowered to some degree after several weeks, while those of 6 other

vessels localized edema space formation and degeneration with detached cells were also seen in the stria vascularis of other animals The most prominent change in the stria was its atrophy found in 2 cochleas of 2 animals as illustrated in Fig 3a

Spiral ganglion cells of 15 cochleas out of 28 showed pathologic features which were most frequently localized in the first turn The commonest changes were nuclear pycnosis and swelling and swelling or diminution of the cytoplasm of the ganglion cells as shown in Figs 6a and 6b Furthermore, swelling degeneration and disappearance of the ganglion cells were found in some animals (Figs 3c and 4b) Fibroblasts and monocytes infiltration were rarely observed among those cells The frequency of the affected ganglion cells was greater in B group than in A group

Pathologic change in eighth nerve was found only in a cochlea as described above

Fernandez (1958) reported that the hemorrhage in the scala tympani near the round window was the artifact due to asphyxia or trauma during dissection and that it was never found in animals killed by intravital fixation In the scala tympani of 3 cochleas of our specimens fixed by intravital perfusion extensive hemorrhages were found especially in one of them all along the cochlea except for the first turn (Fig 7) Consequently this was regarded as a pathologic change Despite the evidence for successful perfusion nubecula or amorphous precipitates were found in either endo or perilymphatic fluid of 7 cochleas Endolymphatic hydrops restricted to the first turn was in only one cochlea These two changes are ordinarily regarded as artifact

The brains and kidneys of these 14 animals and the cochleas of the 5 control animals in both A and B group did not show pathological findings to differentiate distinctly from artifact

Comparing the histological findings with the data of hearing all of the 8 animals whose hearing was impaired over 15 db showed some of the histopathological changes described above Among the other 6 animals threshold shifts were within 10 db 2 did not show any histological changes

Immunological studies

None of the four immunological tests which were applied to sensitized and control animals indicated positive results Namely the anti cochlea anti brain and anti kidney antibodies were not proved in all the animals used

COMMENT

According to Beickert (1961) the histological changes in the guinea pig s cochlea produced by hetero and isologous antibodies were as follows in the spiral ganglion pycnosis of nucleus vacuolation and disintegration (Nissl und Spielmeyersche *Zellerkrankung*) were found most prominently and constantly In both of the outer and inner hair cells swelling of the

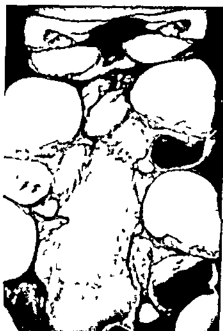


Fig. 7. Guinea pig B 7, right ear. Extensive bleeding in the scala tympani of all turns with the exception of the 1st turn. 25 ×

Histological findings

All the histological findings of 14 guinea pigs are summarized in Table 1. The organ of Corti. Five of 28 ears showed pathological findings. They were not extended to the entire region of the cochlea. In 3 ears, nuclear pycnosis, cloudy swelling and/or slight degeneration of the outer hair cells and their supporting cells were observed (Fig. 2). More prominent changes were seen in 2 ears. Figures 3a, 3b and 3c of the cochlea illustrate disappearance of the outer hair cells, atrophy of the inner hair cells, enlarged Nuel's space, diminished mesothelial cells and degeneration of the supporting cells in the third turn accompanied with atrophy of the stria vascularis in the second and third turns and with degeneration and disintegration of the spiral ganglion cells. The lesion of the organ of Corti localized in the second turn of another cochlea is illustrated in Fig. 4a. The organ of Corti was found in degeneration with its supporting cells accompanying with a considerable amount of cell debris under the atrophied and elevated tectorial membrane. Simultaneously, in addition to the decrease in number of the spiral ganglion cells with the infiltration of fibroblasts and monocytes (Fig. 4b), space formation inside the eighth nerve trunk was seen as illustrated in Figs. 4c and 4d. The extent of the degeneration of the spiral ganglion cells was wider than that of the involvement of the organ of Corti. Therefore, the ganglion cells seems to be involved prior to the organ of Corti.

The stria vascularis in 15 cochleas, especially of A group showed various changes as illustrated in Figs. 5a, 5b, 5c and 5d. As the slightest change, globular formation on the surface was seen in 3 cochleas. Dilated blood

vasodilation globular formation and edema on the surface of the stria vascularis of the quinine intoxicated guinea pigs The degeneration or space formation of our specimens seemed to resemble the stria after a period of exposure to anoxia (Beck & Beickert 1958) and venous obstruction (Perlman & Kimura 1957) Localized atrophy of the stria vascularis was reported in the cochleas of young untreated guinea pigs (Fernandez 1958) in viral labyrinthitis (Lindsay *et al* 1960) in the drug intoxicated cochlea (Hawkins & Lurie 1952 Lindsay, Proctor & Work 1960) in congenital deafness (Ward *et al* 1962) and in the cochleas of sudden deafness patients (Schuknecht *et al* 1962) Fernandez (1958) stated the atrophy might be due to vascular accident Besides 3 out of 28 ears of our specimens presented hemorrhages in the scala tympani and it is well known that the autoimmune reaction is characterized by predilection of perivascular spaces (Kabat Wolf & Bezer 1947) Therefore these findings might be an expression of some vascular lesion in the cochlea

In experimental allergic encephalitis white matter is mainly involved However pathologic changes of the spiral ganglion cells were one of the most frequent findings of our and Beickert s specimens Lesion of the acoustic nerve was found only in one ear and it was not demyelination which was usually found in allergic encephalitis The perivascular infiltration which was also one of the evident features of encephalitis was not presented in either Beickert s (Beickert 1962) or our specimens At the present time we cannot know the cause of the discrepancies of these two organs which are embryologically analogous

The histological changes found by Beickert and us were mostly restricted to some areas in the cochlea or in a few cases to only unilateral ear and Preyer reflex cannot express the hearing ability of unilateral ear However all of the animals whose hearing losses reached over 15 dB showed more or less histo pathological findings in their cochleas

All attempts to prove the anti cochlea antibody in the sensitized animals had failed in spite of use of the most sensitive tests According to Kabat & Mayer (1961) the minimum quantity of antibody detected by both Boyden s and Ovary s tests which were used by us is 0 003 μg N Although the detection of the antibody confirms the evidence of inducement of the autoimmune reaction Beickert also failed to prove the isologous anticochlea antibody by means of microprecipitin method However the failure does not always mean the non existence of the antibody according to the present concepts of immunologists concerned with autoimmune diseases (Kabat *et al* 1947 Frick 1951 Cavelti 1955) because the autoantibody produced which appeared in the blood stream combines immediately with its target organ (autoantigen) Furthermore the quantity of cochlea protein is very small as antigen so that the induced anti cochlea antibody may also be meager

Thus the auditory and morphological changes which were found in only sensitized animals and were not in control animals suggest strongly that the autoimmune reaction was induced in the cochlea Namely the possibility that

nucleus in small groups and increased activity of RNA metabolism were sometimes observed. The epithelial surface of the stria vascularis, especially those of the isologously sensitized animals showed tortuous or bow-shaped swelling which resembled those exposed to anoxia or intensive tone. From his experiment he concluded that in the inner ear structure, especially in the spiral ganglion, the morphologically detectable changes were produced by antigen-antibody reaction in a sense of autoallergic process.

Comparing the results obtained by us with those by Beickert, the resemblance seemed to be only in the feature of the spiral ganglion cells, i.e. nuclear pycnosis, disintegration, swelling of both nucleus and cytoplasm. However, the changes in the hair cells and stria vascularis were more severe in ours than in his specimens. The difference of the degree of tissue damage may be due to the difference of sensitization and histological methods used. In our experiment, as mentioned above, the histological changes in A group injected with our own adjuvant seemed to be slightly different from those in B group done with the commercial one. In the former group, mortality of animals was far larger, and the stria vascularis was more often affected, while in the latter group, mortality was almost a third of that of the former and the spiral ganglion cells were most vulnerable. Beickert sensitized intraperitoneally with the dried and lipoid-free antigen and examined histologically by means of non-decalcified microdissection technique, which is excellent to find delicate changes of the respective cells or tissues in the cochlea, but is not able to obtain the entire view of it. In addition to his findings we could reveal space formation in the eighth nerve, bleeding in the scala tympani and a large amount of cell debris in the endolymph being accompanied with degeneration of the organ of Corti by means of routine histological method.

As to the lesions of the organ of Corti, pathological changes were found in 5 out of 28 ears and 2 of them (Figs. 3, 4) were so peculiarly damaged that the analogous picture was not found in the literature concerned with acoustic trauma (Ruedi & Furrer 1951, Ruedi 1954, Arai 1952), drug intoxication (Hawkins & Lurie 1952, Hennebert & Fernandez 1959, Ward & Fernandez 1961), vascular obstruction (Perlman & Kimura 1957, Davis *et al.* 1958), viral labyrinthitis (Lindsay *et al.* 1953, Lindsay & Hemenway 1954, Lindsay *et al.* 1960) and congenital deafness (Lurie 1941, Altmann 1950, Ward *et al.* 1962). It, however, requires further investigation to determine whether these are the characteristic changes which were produced by only isoimmune reaction or not, because of a minority of the cases.

Beickert stated that histological changes of the hair cells were caused possibly through the stria vascularis and endolymph and that the nutritive disturbance of any etiology resulted in the same morphological change in the cochlea. In the stria vascularis of our specimens, globular formation, dilated blood vessels, edema, space formation, degeneration and atrophy were found. The features analogous to these findings could be found in the literature of other inner ear pathology. Hennebert & Fernandez (1959) found

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inner ear disease of one ear affects the opposite ear is experimentally assumed.

Clinically, Lehnhardt (1958) made an assumption that anti-organ of Corti antibody might be an etiological factor of bilateral sudden deafness. According to Schuknecht *et al.* (1962), both ears are involved in less than 20 per cent of the sudden deafness patients and recovery of hearing occurs in about 50 per cent. Although the results obtained from the present experiment are still far from clinical application, it is of interest that the partial recovery of impaired hearing was observed in some of the sensitized animals.

Finally, further research should be made in order to obtain stronger evidence to clarify the relationship with clinical picture of inner ear deafness.

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ZUSAMMENFASSUNG

Durch Injektion von mit *Freund*schen Adjuvantien emulsierter Meerschweinchen Cochlea kann man bei anderen Meerschweinchen eine akustische sowie histologische Veranderung erzeugen, wie sie als Ausdruck einer Isoimmunisation zur Cochlea interpretiert werden muss, obwohl uns der Nachweis des anti-cochlealen Antikorpers nicht gelang. Der Adjuvant allein bewirkt keine positive Reaktion.

Die histologischen Hauptveranderungen wurden in dem spiralen Ganglion und der Stria vascularis gefunden. In etlichen Fallen wurden Blutungen in der Scala tympani und Desintegration des Cortischen organs beobachtet. Diese Veranderungen stimmten im allgemeinen mit den akustischen Schwellen-Verschiebungen uberein.

Aus diesem Grunde sieht man Moglichkeiten, dass als Folge einer autoimmunen Reaktion die Erkrankung des inneren Ohrs in einer Seite das andere Ohr beeintrachtigt.

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THE NON-AUDITORY LABYRINTH AND POSITIONAL ALCOHOL NYSTAGMUS

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It has been previously established that positional alcohol nystagmus (PAN) is dependent on the presence of the non-auditory labyrinths, even though the site of action of the alcohol is thought to be central. The relative importance of the semicircular canals and the otoliths in PAN was investigated by experimental surgery. When all six canals were inactivated in cats without interfering with otolith function, PAN no longer occurred.

Since alcohol-induced nystagmus was first reported by Flourens in 1828 it has been the subject of considerable investigation. In 1913 Rothfeldt gave alcohol to rabbits by stomach catheter and noted that nystagmus developed only when the head was held in the lateral position (right or left side down). In 1930 de Kleyn & Versteegh (1930) verified these findings and made the significant contribution that such nystagmus could not be induced after bilateral labyrinthectomy; they were unable, however, to attribute the lack of response specifically to the absence of either the semicircular canals or the otoliths. More recently Aschan *et al.* (1956) and Bergstedt (1961) have thoroughly investigated positional alcohol nystagmus (PAN) in man, recording the effects by electronystagmography. These authors reported two distinct phases in its development, namely PAN I when the quick component of the nystagmus was directed toward the side that was down, and PAN II in which the direction of the quick component was toward the side that was up. In human subjects PAN I was observed about 30 minutes after ingestion of alcohol and lasted for as long as three hours. This was followed by an intermediate period lasting about 90 minutes during which period only irregular eye movements were seen. The intermediate phase was succeeded by PAN II which lasted about six hours. It was interesting to note that PAN II often began after all trace of alcohol had disappeared from the blood. The duration of nystagmus in either phase increased with an increase in the quantity of alcohol consumed. It would appear from the work of Aschan and others that alcohol acts centrally to cause PAN but that the presence of the non-auditory vestibular end organs is essential in some way which is not fully understood. Harris, Guedry & Graybiel (1962) found no PAN

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que The results of tests for otolith function were essentially the same as in the pre operative state excepting the response to dropping from the inverted position which involves a response by the otoliths and the semicircular canals It was concluded that the otoliths still functioned normally

Stage I of positional alcohol nystagmus was not observed in the operated animals after the ingestion of alcohol This result is in marked contrast to that obtained in the same animals before operation and was obtained despite the fact that the dose and administration of the alcohol were the same in all experiments Furthermore, none of the operated animals vomited

CONCLUSIONS

1 Inactivation of the semicircular canals in cats eliminated positional alcohol nystagmus

2 The work reported does not permit a conclusion on whether or not the presence of functional otoliths is necessary for the occurrence of positional alcohol nystagmus

ZUSAMMENFASSUNG

Es ist schon früher gezeigt worden, dass der Alkohol Lagenystagmus ausgelöst werden kann nur wenn der periphere Vestibularapparat intakt ist

Trotzdem wird angenommen dass die zentrale Wirkung des Alkohols aus schlaggebend ist

Die Bedeutung der halbzirkelförmigen Kanäle einerseits und des Otolithapparates andererseits für den Alkoholnystagmus ist experimentell untersucht worden.

Wenn alle sechs Kanäle ausgeschaltet wurden, mit erhaltener Otolithenfunktion, konnte ein Alkohol Lagenystagmus nicht mehr ausgelöst werden

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in deaf human subjects suspected of having residual otolith function (and apparently no canal function).

It is the object of this paper to describe some experiments carried out to determine the relative importance of the semicircular canals and of the otoliths in the occurrence of PAN.

METHODS

Eight healthy cats were selected because of their normal vestibular function and their pre-operative susceptibility to PAN. The semicircular canals and the otoliths of each cat were tested according to the procedure described by Money & Scott (1962). These tests include rotation in the planes of the horizontal and vertical canals and three different otolith tests (slow tilting, linear accelerations and drop tests). Following these pre-operative tests all six semicircular canals of each cat were plugged (Money & Scott 1962) without encroaching on the ampullae or the vestibule.

About two weeks post-operatively, the vestibular function tests were repeated. Two weeks and again four weeks post-operatively the cats were tested for PAN.

The pre- and post-operative tests for PAN were carried out by the following procedure. The cat was secured to a board and a 20% solution of ethanol in water (1.6 g ethanol per kg of body weight) was administered by gavage through a PE 100 polyethylene nasal tube. The animal was then freed and tested for positional nystagmus by gently holding the head in the appropriate positions.

RESULTS

(a) *Pre-operative Tests for PAN*

PAN I began about 13 minutes after alcohol ingestion and averaged one hour and 45 minutes in duration. In the lateral position the quick component of PAN I was directed toward the side that was down, whereas in the supine position (head elevated with hard palate upright and the nose pointed up) PAN was vertical with the quick component directed toward the lower lid. It was noted particularly that both the magnitude and direction of this nystagmus was dependent upon the position of the head. Thus the magnitude of the nystagmus was maximum with the hard palate at 90° to the floor and was less in positions reached by rotating the head slowly backward from this position. In positions attained by rotating the head still further backward many of the cats exhibited a revival of vertical nystagmus but with the quick component directed toward the upper eyelid.

PAN II was not observed in these animals during the six hours following alcohol ingestion. Vomiting occurred in three of the animals.

(b) *Post-operative Tests*

The tests of canal function demonstrated that all six semicircular canals in each cat had been rendered non-functional by the canal blocking techni-

jue The results of tests for otolith function were essentially the same as in the pre operative state excepting the response to dropping from the inverted position which involves a response by the otoliths and the semicircular canals It was concluded that the otoliths still functioned normally

Stage I of positional alcohol nystagmus was not observed in the operated animals after the ingestion of alcohol This result is in marked contrast to that obtained in the same animals before operation and was obtained despite the fact that the dose and administration of the alcohol were the same in all experiments Furthermore, none of the operated animals vomited

CONCLUSIONS

1 Inctivation of the semicircular canals in cats eliminated positional alcohol nystagmus

2 The work reported does not permit a conclusion on whether or not the presence of functional otoliths is necessary for the occurrence of positional alcohol nystagmus

ZUSAMMENFASSUNG

Es ist schon fruher gezeigt worden, dass der Alkohol Lagennystagmus ausgelöst werden kann nur wenn der periphere Vestibularapparat intakt ist

Trotzdem wird angenommen dass die zentrale Wirkung des Alkohols aus schlaggebend ist

Die Bedeutung der halbzirkelformigen Kanale einerseits und des Otolithapparates andererseits fur den Alkoholnystagmus ist experimentell untersucht worden

Wenn alle sechs Kanale ausgeschaltet worden mit erhaltener Otolithenfunktion, konnte ein Alkohol Lagenystagmus nicht mehr ausgelost werden

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PARTIAL LARYNGECTOMY IN THE TREATMENT OF CANCER OF THE LARYNX

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Out of 21 patients treated by partial laryngectomy for cancer of the larynx, nine were alive and free from recurrence after a 5-year observation period. Seven died from recurrence and five from other causes, but with no signs of recurrence, less than 5 years after the operation. The functional results were definitely satisfactory.

Partial laryngectomy comprises a number of surgical interventions, ranging from simple laryngofissure (opening of the larynx by a median incision followed by excision of the tumour and surrounding soft tissue, but without resection of the laryngeal cartilage) to resection of nearly two-thirds of the larynx. The partial laryngectomies are often divided into vertical and horizontal procedures, while the vertical are subdivided into saggital and frontal. However, all transitional forms exist between the two latter.

In 1878 Billroth undertook the first hemilaryngectomy (hemilateral removal with opening along the midline anteriorly and posteriorly). During the following years only few surgeons adopted the method, as the mortality was high and the curative results poor. By the end of the nineteenth century Gluck (1913) improved the technique, by plastic covering of the large wound, among others. At the same time he restricted the indications for this operation. Gluck (1913) thereby obtained a fall of the mortality to few per cent and considerably improved curative results. About 1925 Hautant devised a new method, which was gradually adopted by various other surgeons and has been described in detail by Ombrédanne (1930) (the larynx is not opened along the midline, but 5–6 mm from this on the unaffected side. On the other hand, the posterior muscle bearing parts of the thyroid cartilage and the arytenoid cartilage on the affected side are preserved). Especially the functional results were greatly improved by this technique. Hautant's technique in more or less modified forms is employed by most surgeons to day, e.g. Leroux Robert (1957). An essential improvement, suggested within recent years by Figi (1953), among others, is that of covering the surface of the wound by a free graft. This procedure makes it possible to remove up to two thirds of the larynx without risking collapse or stenosis of the laryngeal cavity. Alonso (1950, 1957) has within recent years developed the technique of partial horizontal laryngectomy, i.e. removal of the part of the larynx situated above

the vocal cords In suitable cases (cancer of the vestibule, involving the inferior part of the epiglottis and the anterior parts of the vestibular folds) this gives favourable therapeutic as well as functional results

PRESENT MATERIAL

Within the past 10 years 33 patients have been submitted to partial laryngectomy in the Ear Department of the Finsen Institute, in 5 cases owing to cancer of the pyriform sinus and in 28 to endolaryngeal cancer 21 of the latter group have been observed for 5 years These constitute the series described in greater detail below One of these 21 may have been a case of metastatic cancer of the larynx

TABLE 1 *Age incidence*

Age	No of cases
40–49	4
50–59	3
60–69	12
70–79	2

The age incidence is shown in Table 1 The ages ranged from 47 to 77, averaging 60 years All the patients were men All the patients gave hoarseness of from 1 month to 3 years duration as the first and only symptom 15 patients had had symptoms for less than 4–5 months before being referred to the Department

Six patients had previously received X ray treatment with a full cancericidal dose according to a modified fractional Coutard technique In these cases it was thus a question of recurrence or a residual tumour The recurrence was demonstrated from 4 months to 4 years after the X ray treatment In one case X rays were given postoperatively in full dose

The sites of the tumours are seen in Table 2 In most of the cases the tumour was localised in one half of the larynx In a small proportion it extended as far as or a little past the anterior commissure Posteriorly the tumour reached the vocal process only in a single case slightly further back

One case was diagnosed histologically as fibrosarcoma, while all the others were squamous cell carcinomas of medium grade differentiation

OPERATIVE TECHNIQUE

The operation was in all the cases started by tracheotomy in local anaesthesia Next the patient was submitted to general anaesthesia through the tracheal cannula In five cases anterior (frontal vertical) resection was performed in the remaining cases a chiefly lateral resection i e a modified hemilaryngectomy according to Hautant with removal of one third to one

TABLE 2. *Partial laryngectomy. 5 year observation time*

Site	No.	Alive and recurrence free	Dead from cancer	Dead from other cause with no signs of cancer
True vocal cords	5	2		3
Subglottis	7	3	4	
True vocal cords + subglottis	4	2	1	1
False vocal cords	1	1		
True + false vocal cords	2		1	1
True + false vocal cords + subglottis	1	1		
Over the anterior commissure	1		1	
Total	21	9	7	5

TABLE 3. *Partial laryngectomy. 5 year result*

Total number	21
Indeterminate	5
Determinate (21-5)	16
5 year result 9/16	56.3 %

half of the unaffected half of the larynx in addition to the entire affected half. The surgeon was here guided by the grossly visible extension of the tumour as well as by the findings in frozen sections and aimed at keeping at a suitably great distance from the tumour in all directions. In one case a cervical gland was dissected, as the operation revealed a well defined, movable glandular metastatic growth. In none of the other cases were glandular metastases palpable at the time of operation, and cervical gland dissection was therefore omitted. The first six patients operated on had no graft implanted, while all the subsequent operations included implantation of a free graft, at first on a mould of Stent's mass, and later on a finger stall tampon, this being easier to remove afterwards.

RESULTS

(See Tables 2 and 3)

One patient died in relation to the operation. He had been suffering in advance from renal failure, which exacerbated and caused death from uraemia 20 days after the operation (the patient has been registered as dead from cancer). Five patients died less than 5 years after the operation, but without signs of recurrence (indeterminate). Seven patients died from or with recurrence *of cancer. In only one of these was there local recurrence* (the patient was submitted to total laryngectomy, but died later from metastases), while the remainder had cervical gland metastases. However, two of these also had cancer tissue round the tracheostoma 3 months and 3½ years

respectively after the operation. In the former this was possibly due to lymphogenous spread, while in the latter presence of fresh cancer was, perhaps, more likely. In none of these two cases would a better result have been achieved by total laryngectomy. Two patients developed distant metastases in addition to cervical gland metastases, in one of these to the liver and lungs, in the other only to the lungs.

Nine patients were alive and free from recurrence 5 years after the operation. One of these, however, experienced local recurrence just over 5 years after the partial laryngectomy. Total laryngectomy was done and the patient has been free from recurrence 3 years and 4 months after the latter operation.

The tracheal cannula could be removed after greatly varying intervals, the soonest on the fifth day, in the majority within 3 weeks of operation. Among the nine living patients with no recurrence only one wore a permanent cannula (speech cannula). The voice was good and useful in all the cases, though more or less hoarse. Like other writers we have occasionally seen formation on the operated side of a bracket like projection acting as a fixed vocal cord. The working capacity was normal in six cases and somewhat reduced in three (in two of these mainly owing to a high age, and in the third on account of mental illness).

Of the remaining patients six could do permanently without the cannula while six had to have it re-inserted after shorter or longer intervals.

DISCUSSION

Though many laryngologists are still opposed to partial laryngectomy (excepting laryngofissure), either because they doubt about its value as a radical operation or because they regard the functional results as too poor, a steadily increasing number adopt this procedure. Among the majority of these, however, the stated operation still represents *only a small*, though rising percentage of the total number of laryngectomies owing to the difficulty with regard to the indications. Various factors (the site, extension and degree of differentiation of the tumour, possible glandular metastases, the patient's *age, occupation* and psyche, previous radiotherapy, etc.) influence the choice of operation and make it difficult to generalise as to indications.

It is our impression that moderate overlapping of a vocal cord cancer to a *false* vocal cord is no contraindication to partial laryngectomy, as also stated by Mounier Kuhn (1961) and by Piquet (1957). In contrast to Lalbe Hansen and Svane Knudsen (1963) we did not have poorer *results in the cases* where a vocal cord cancer occupied or to a limited extent *even crossed* the anterior commissure. This is, however, probably due to our resections having been more extensive.

Cancer of the larynx is *in our* Department treated in collaboration with radiologists from the Radium Centre. Within the *period* from which the present series has been collected laryn*gofissure* has not been employed for a small malignant tumour on a movable vocal cord. Such cases were sub-

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mitted to radiotherapy, which gives the same therapeutic, but better functional results. Operation was performed in cases of recurrence (or residual tumour). The same was true of recurrences after radiotherapy of more extensive tumours.

Six of the 21 patients had, as stated above, been treated first by a full cancericidal dose of X-rays. These cases gave occasion to no particular troubles, neither during the operation nor postoperatively, except for a somewhat delayed healing of the wound. Within recent years larger volume doses have been employed in the treatment of the fairly big endolaryngeal tumours. Even though in such cases circumscribed recurrences or residual tumours indicated partial laryngectomy, the results were often seen to be interfered with by oedema and necrosis, preventing decannulation of the patient. At the same time observation of the patients with a view to recurrence was rendered difficult and required many direct laryngoscopies and biopsies. These patients would doubtless have been better served with total laryngectomy.

ZUSAMMENFASSUNG

21 Patienten wurden wegen Kehlkopfkrebses mit Laryngectomia partialis behandelt. Neun leben rezidivfrei 5 Jahre nach der Operation. Sieben sind an Rezidiv gestorben. Fünf sind an anderen Ursachen weniger als 5 Jahre nach der Operation gestorben, aber ohne Zeichen zu Rezidiv. Das funktionelle Resultat war völlig befriedigend.

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PERCEPTION OF DICHOTIC AND MONAURAL VERBAL MATERIAL AND CEREBRAL DOMINANCE FOR SPEECH[1]

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The primary purpose of the present investigation was to determine whether asymmetry between sides occurs in the recognition of verbal material under conditions of dichotic or monaural presentation of words. In the first experimental procedure, different filtered PB words (one to each ear) were presented simultaneously to 24 young adults with normal hearing, and the subject responded to both stimuli. In a second condition, the same filtered words were delivered simultaneously to each ear but the subject attended to only the word in one or the other ear. During the final presentation, the filtered words were delivered monaurally. Pair digits, as reported by Kimura (1961 a, 1961 b) were also presented simultaneously to each ear and the subject was instructed to respond to all the digits.

The results of both the simultaneous presentation of digits and filtered lists demonstrated that significantly more words were recognized from the right ear, contralateral to the dominant hemisphere for speech in this group, than from the left ear. But when the same filtered words were delivered monaurally, as in the Calearo & Antonelli (1963) investigation, the results were identical for each ear. The findings substantiated the suggestion by Kimura (1963) that when competition occurs between auditor pathways, ipsilateral and contralateral to the dominant hemisphere for speech, asymmetry between sides is observed.

In a recent investigation by Calearo & Antonelli (1963) it was reported that cortical integration of verbal messages was symmetric and functionally equivalent for both hemispheres. Their conclusions were based on the findings that normal subjects showed no difference between the two ears for the reception of filtered or interrupted speech. On the same test, discrimination ability was also found to be decreased equally in ears contralateral to the hemisphere where temporal lobectomies were performed. The investigators suggested that the dominance of the left cerebral hemisphere for speech had no significant influence on the results and thus that both hemispheres were functionally symmetrical for the perception of verbal stimulation.

Other investigations by Kimura (1961 a, 1961 b) have shown that the left

[1] This investigation was supported by Grant B-4019 to Victor Goodhill, M.D., from the United States Public Health Service.

hemisphere plays a predominant role in the recognition of verbal stimuli when different material is presented simultaneously to the two ears and the subject is instructed to respond to both messages. In these experiments, digits were delivered in pairs of six, three digits in one ear and three in the other The subject merely reported the numbers he heard in both ears in any order he wished. Both normal subjects and unoperated epileptic patients with speech represented in the left hemisphere consistently recognized more digits from the right ear than from the left. Likewise, in subjects where the right hemisphere was dominant for speech, superior responses were obtained from the left ear. When digits were alternated between ears, no significant differences were observed between the sides. The validity of the digits test was established on 120 unoperated patients with epileptogenic lesions, 107 with speech represented in the left and in 13 patients found to have speech in the right hemisphere by the amytal injection method of Wada & Rasmussen (1960).

Some conflict seems to exist between the conclusions reached in the above investigations concerning the role the dominant hemisphere for speech plays in the perception of verbal stimuli. A major difference exists in the presentation of verbal materials between the tests administered by Calearo and Antonelli and those used by Kimura In the former, all words were delivered to one ear, while in the latter different digits were presented to the two ears simultaneously and a response was required to both sides Kimura (1963) has suggested that competition between auditory pathways, ipsilateral and contralateral to the dominant hemisphere for speech, was necessary before the asymmetry between sides would be observed A corollary to this suggestion would appear to be that if verbal stimuli are presented monaurally the asymmetry would not be found Thus, in the present investigation, both dichotic and monaural presentations of filtered words were administered to each subject in order to determine the presentation conditions under which the perception of verbal material was related to the dominant hemisphere for speech

Subjects

The subjects in the present investigation were 24 young adults with normal hearing In order to be admitted to the experimental group, each subject was screened audiometrically at a hearing level of 10 dB re USPHS norm at the frequencies of 125 cps, 250 cps, 500 cps, 1000 cps, 2000 cps, and 6000 cps Of the 24 subjects, there were 18 females and 6 males The mean age of the subjects was 16 8 years with a range from 15 to 19 years Although dominance for motor activities is not necessarily linked to speech dominance, attempts were made to use right handed individuals in this investigation In this regard, Goodglass & Quadfasel (1954) reported that left cerebral laterality for speech is more prevalent than right-handedness but that right cerebral laterality for speech is much less prevalent than left-handedness All subjects

were right handed in the present study, except for two who gave reports of ambidexterity These subjects were included in the study since they recognized more words presented to the right ear than to the left on the digits test Such a result is consistent with findings for individuals with left cerebral dominance for speech

Test Material

Three measures of the subject s ability to understand speech were employed in the present investigation (1) spondee words, (2) filtered PB 50 words, and (3) digits The spondee word list consisted of the 22 words suggested by Bowling & Elpern (1961) which were considered to be relatively homogeneous in intelligibility These words were recorded in random order on one channel of a dual channel Sony 777 tape recorder via a Sony Model C 37A Condensor Microphone and Power Supply Unit

Two lists of phonetically balanced words were also recorded on one channel of the tape recorder employing the same apparatus, as used for the spondee recordings The taped words were then reproduced on film by a professional studio[1] one group of fifty words on one channel the others on a second channel By appropriate splicing the words from each channel appeared at five second intervals The splicing technique permitted the investigator to pair the words from each list so that both began at exactly the same time Recall that in the Kimura investigations simultaneity of different digits at each ear was required if asymmetry was to be demonstrated

In a final preparatory step the words were passed through a low pass filter set at 1000 cps with a rejection rate of 18 dB per octave band Thus the experimental tape consisted of two lists of filtered PB words recorded in such sequence that each word on one channel began at the same time as a paired word on the second channel

The third experimental tape was prerecorded[2] and consisted of six digits taped in such a way that half the digits were presented through one channel and the other half simultaneously on the second channel On 12 groups as described above the three paired digits on each channel were presented at half second intervals while on six other groups digits arrived at one and one half second intervals As a result there were 18 groups of six digits three on each channel or a total of 54 digits were presented to each ear Although the original digits test consisted of 96 items only the three groups of items which were most sensitive to the dominance factor were used in the present investigation

[1] Grateful appreciation is extended to Revue Studios for their aid in the preparation of this tape

[2] The digits were recorded from the original tapes employed by Kimura (1961a 1961b) Appreciation is expressed to Dr Doreen Kimura for permitting use of these tapes and for her helpful suggestions in the present study

Apparatus

Taped spondee and filtered PB words were delivered to the subjects via a dual channel Sony 777 Tape Recorder the outputs of which fed a Grason Stadler Type 162 Speech Audiometer. Each channel of the speech audiometer was connected to one of two TDH 39 earphones mounted in MX 41/AR cushions. All experimental tests were carried out in a double walled Industrial Acoustics Booth 1200 series.

The acoustic signals developed by the earphones from taped pure tones at octave frequencies from 125 cps to 4000 cps were measured before each testing day. The measurement apparatus consisted of a Bruel Kjaer DB10f0 6 cc coupler, Bruel Kjaer Condenser Microphone Type 4132 and a Bruel Kjaer Spectrometer Type 2112. The experimental equipment was found to be stable throughout the testing period.

Methods

Thresholds for spondee words were obtained on each ear of a subject by the Up and Down method described by Jerger *et al* (1959). Subsequently all experimental tests were delivered to the subject's ears at levels above the obtained spondee thresholds. Each subject received a series of four experimental tests, the digits and three forms of the filtered word lists. The original filtered PB lists were re-ordered so that the same pairs of words could be presented dichotically a second time to each subject. In a typical test session the subject was instructed (1) to respond to the words in both ears (Dichotic II), (2) to repeat only the words in either the right or left ear and ignore the competing word (Dichotic I), and (3) to repeat the word which appeared monaurally in either his right or left ear (Monaural). If the subject was required to respond to the right ear in the Dichotic I and Monaural conditions on the first presentation, he was then instructed to reiterate the words in the left ear when these conditions were repeated.

The digits test was administered immediately after the spondee threshold was obtained on half the subjects and as the final test following the filtered presentations to the other subjects. All digits were delivered at sensation levels of 20 dB above the spondee thresholds, while the filtered words were delivered at sensation levels of 40 dB above the spondee thresholds. In both cases, levels were chosen which were sufficiently difficult for normal subjects to score 90 per cent on the digits tests and approximately 60 per cent on the monaural filtered words test. In preliminary investigations with the digits test, words were presented at sensation levels of 40 dB. At these levels normal hearers obtained near perfect scores so that the dominance effect was not always observed as clearly as when the digits were delivered at a lower sensation level.

The three filtered presentations were completely counterbalanced among

TABLE 1 *Comparison of the mean correct responses in percentages for each ear for the various experimental tests and conditions*

Test/Condition	Right Ear Mean	Right Ear S D	Left Ear Mean	Left Ear S D	Mean Diff Between Ears	t
Filtered Words						
Dichotic II	40 3	13 5	33 3	11 9	7 0	2 10*
Dichotic I	45 4	11 0	41 0	10 1	4 4	1 22
Monaural	57 8	8 6	57 6	9 1	0 2	0 09
Digits	92 6	5 8	86 4	6 8	6 2	5 29**

* $p < .025$ for df = 23
** $p < .001$ for df = 23

the subjects The earphones were reversed from one subject to the next so that half the subjects heard the words on Channel I of the apparatus in the right ear and half in the left ear and conversely for the words on Channel II

RESULTS

The data from the various experimental conditions are presented in Table I The number of correct responses on each test were transposed into appropriate percentages and the differences in the mean percentages between ears were compared by use of t tests for correlated means as described by Edwards (1958) The results of the spondee thresholds do not appear in the table since they were employed in this investigation only as references to establish the level at which the experimental lists were to be delivered The mean spondee threshold for the group was 22 8 dB re 0 0002 dyne/cm² for the right ear and 22 2 dB re 0 0002 dyne/cm² for the left ear

The results of the digits test demonstrate that more digits were recognized from the right ear than from the left ear The superiority of 6 2 per cent was statistically significant beyond the 001 level and agrees well with results of previous investigations where digits were also employed

When the filtered PB words were delivered simultaneously to each ear (Dichotic II condition) and the subjects were instructed to respond to the words from both sides the responses from the right ear were again more efficient than those from the left ear The mean difference of 7 per cent which favored the right ear was statistically significant at the 02 level In the second filtered word condition (Dichotic I) more words were recognized in the right ear but the difference of 4 4 per cent was not statistically significant Recall that in this measurement the subject received the same paired words as in a Dichotic II test but was instructed to respond to only one ear Finally when the same filtered words were presented monaurally, the results

were practically identical for both sides, 58.8 per cent for the right ear and 58.6 per cent for the left ear.

It is apparent from the above data that the responses to the words presented to the right ear, that is, the one contralateral to the dominant hemisphere for speech, were superior to those from the left ear under conditions where both ears received different stimuli simultaneously. The result was observed both for the digits and for the filtered speech words. When the subject responded to the word in one ear only and therefore was permitted to ignore the stimulus on the opposite side (Dichotic I), the responses from the right ear maintained a slight superiority, but the difference between sides did not reach a level of statistical significance. Finally, when filtered words were delivered monaurally, the responses from each side were equivalent, similar to the findings of Calearo & Antonelli (1963) on their normal subjects

DISCUSSION

The significant difference between the responses from the two ears on the Dichotic II procedure and the digits tests favored the right ear and substantiated the suggestion by Kimura (1963) that words are more efficiently recognized from the ear contralateral to the dominant hemisphere in the condition where different filtered words are presented to two ears simultaneously and the subject is instructed to respond to both stimuli When the filtered words were delivered monaurally, the discrimination scores were almost identical for each ear and agreed with the findings of Calearo & Antonelli (1963) on normal listeners A similar result has also been reported elsewhere with digits as the verbal stimulus Kimura (1961 a) observed that when digits were alternated from one ear to another, no asymmetry was found between the responses from the two ears At the same time the simultaneous dichotic presentation of the digits produced a right-ear effect Therefore, it appears that competition between the contralateral and ipsilateral pathways to the dominant hemisphere for speech is required before the functional asymmetry can be demonstrated

A further notable result was the finding that more words were recognized from the right ear than from the left, even under conditions where the subject was instructed to repeat the word on one side only (Dichotic I) Apparently the mere presence of a verbal message in the non-test ear provided sufficient competition between sides to cause slightly superior, although statistically nonsignificant, responses from the ear contralateral to the dominant hemisphere

Another observation is of interest in the results from Table 1 Reference is made here to the difference in the total scores between the Dichotic I and Monaural conditions The mean score on the right ear was 12 4 per cent greater for the Monaural condition than for the Dichotic I presentation and 16 6 per cent higher on the left ear For both ears combined, the average dif

ference scores between the two conditions was 14.5 per cent favoring the Monaural presentations. In spite of the separation afforded by the attenuation of the head, the presence of a similar stimulus in the opposite ear has a disturbing interference effect on the total response of the test ear. Since both ears in this study were practically identical for pure tone and speech thresholds and further, since the intensity levels of the competing words were weak enough so that peripheral cross masking should be ruled out, the interference presumably is not of a peripheral origin. No doubt the effect on the test ear of a competing message in the opposite ear will vary from the present results as the competing stimulus becomes different from the primary signal. In the present study, this effect may be maximal since stimuli in both ears were similar.

The investigations of Bocca *et al.* (1957) and Jerger & Mier (1960) have demonstrated the usefulness of distorted speech and competing message tasks in diagnosing impairments affecting the central auditory system. But as Calearo & Antonelli (1963) have pointed out, the influence of the dominant hemisphere for speech on discrimination is a consideration which must be determined if these tests are to be employed for diagnostic use. The results of the present study provide some additional information concerning the type of presentations which would be sensitive to central auditory system impairment and yet are not unduly affected by the dominance factor. One obvious implication arising from the present study is that responses from tests employing monaural verbal messages will not be demonstrably affected by dominance for speech.

Jerger & Mier (1960) have included two competing message tasks in their diagnostic test battery. In both tests the patient responded to only one signal while a vastly different verbal message was delivered to the opposite ear. These tests are similar to, although not as difficult as, the Dichotic I condition of the present investigation. Recall that the difference in response between ears on the Dichotic I condition was small (4.4 per cent) and did not reach a level of statistical significance. Thus somewhat more favorable intelligibility scores might be anticipated for the ear contralateral to the dominant hemisphere for speech if the diagnostic test is a competing message task. But the effect should be slight and certainly much smaller than the effects of central auditory impairment on discrimination as reported by Jerger and Mier.

ZUSAMMENFASSUNG

Der Hauptzweck dieser Untersuchung war herauszufinden, ob Asymmetrie der Seiten im Gehörvermögen beim Erkennen gesprochener Wörter vorkommt, und zwar unter den Voraussetzungen zweiseitiger oder einseitiger Wiedergabe. Während des ersten experimentellen Vorgangs wurden verschiedene filtrierte PB Wörter gleichzeitig (eines in jedes Ohr) 24 jungen Erwachsenen mit normalem Gehör vorgesprochen und die Versuchspersonen reagierten auf beide Reize.

Während des ersten experimentellen Vorgangs wurden verschiedene filtrierte PB Wörter gleichzeitig in jedes Ohr gesprochen, aber die Versuchspersonen reagierten nur auf das Wort in dem einen oder in dem andern Ohr. Während des darauffolgenden letzten Vorgangs wurden die filtrierten Wörter einseitig gegeben. Auch zweistellige Zahlen wurden gleichzeitig in jedes Ohr gesprochen, wie von Kimura berichtet (1961a, 1961b), und die Versuchsperson wurde instruiert auf alle Zahlen zu reagieren.

Die Ergebnisse der gleichzeitigen Wiedergabe von Zahlen und filtrierten Listen zeigte, dass erheblich mehr Wörter vom rechten Ohr erkannt wurden, kontralateral zur die Sprache dominierenden Hemisphäre, als vom linken Ohr. Doch wenn dieselben filtrierten Wörter einseitig zugeführt wurden, wie bei dem Calearo und Antonelli Versuch (1963), waren die Ergebnisse für jedes Ohr identisch.

Die Ergebnisse erhärten die Anregung Kimuras (1963), dass Asymmetrie der Seiten festgestellt werden kann, wenn Gehörwege, die ipsilateral zur dominierenden Hemisphäre für Sprache liegen, mit denen konkurrieren, die sich kontralateral auf der entgegengesetzten Seite befinden.

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CONGENITAL TRACHEAL DIVERTICULUM

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A case is reported of congenital tracheal diverticulum with a cough as the only symptom The development, diagnosis, and symptomatology are reviewed on the basis of the literature The conclusion must be justified that a cough of long standing may be due to a tracheal diverticulum and that such can only be diagnosed by careful inspection of the tracheal wall through a bronchoscope

Tracheal malformations are infrequent findings in the clinical routine This is due to the fact that the defects as such are rare and that the majority cause no or only vague symptoms being therefore seldom diagnosed

The progress made during the past few decades within thoracic surgery and endoscopy has however thrown some light on these affections which formerly were known chiefly as accidental patho anatomical findings

The tracheal abnormalities have been divided according to a slight modification of Jordan s (1939) classification

1 Agenesis
2 Constriction
3 Dilatation
4 Evaginations
   a cyst
   b tracheocele
   c diverticulum
   d tracheal bronchus
5 Fistulae
6 Abnormal bifurcation

As is well known the trachea develops about the fifth embryonic week A vertical *groove is formed in the* anterior wall of the foregut The groove gradually *deepens and its* lips fuse converting the groove into a tube Superiorly it *communi*cates with the part of the foregut forming the pharynx while inferiorly two lung buds arise covered by mesenchymal tissue These proliferate divide and become canalised developing into bronchi and lungs

On this basis the various congenital malformations are easily *explainable* The evaginations may arise either *in* consequence of an abnormally early and l al normally high division *of the primary* lung bud or by further development of a super numerary anlage

In the Ear Department of the Finsen Institute we have had a patient with a tracheal evagination diagnosed bronchoscopically. The case history is so typical in several respects as to justify publication.

CASE REPORT

The patient, a 50 year old accountant, was in December 1962 referred for out-patient examination to the Ear Clinic owing to a bad cough of several months duration. The patient now and then coughed up clear sputum.

The patient had previously been well in the main, more particularly he had no symptoms from the airways. Allergic reactions were known neither in the patient nor in any of his relatives. Examination at a tuberculosis test clinic shortly before transfer to the Ear Clinic had revealed no abnormality.

Neither otologic nor general clinical examination disclosed any cause of the patient's symptoms. X-ray of the thorax, haemoglobin test, counts of red and white blood cells, colour index, and differential counts showed normal conditions. W.R. negative, E.S.R. 7.

On Jan. 2, 1963, bronchoscopy was performed, which showed normal conditions. Secretion was drawn from the bronchial stems for culture and examination for tumour cells. The former gave non-haemolytic streptococci sensitive to penicillin. Microscopic examination of secretion from the right bronchial stem revealed "smear rich in cells from the deep airways with numerous lymphocytes, no signs of malignancy", and from the left "specimen containing vacuolated, distended cells with a distinct nucleus, not definitely malignant, but here and there reminiscent of highly vacuolated macrophages. The possibility of mucoid carcinoma cannot be excluded".

After having received this description we found it most correct to repeat the bronchoscopy after a short observation period, as the symptoms persisted unchanged.

On March 3, 1963, the patient was again submitted to bronchoscopy. This time an opening was found in the right lateral wall of the trachea about 4 cm above the bifurcation. The opening had a diameter of about 1 cm and was at first supposed to be a constricted right bronchus, the lower limit being regarded as a displaced carina. The true facts of the case were soon realised, however, as the opening was found to lead into a pouch, and a normal appearing carina was seen a little further down.

The diverticulum had smooth walls and a red, irritated mucous membrane which bled when touched. It was judged to be about 2 cm long. As was the case at the first bronchoscopy, the bronchial tree itself was also now seen to be normal. More particularly, the right upper lobe bronchus was divided normally into three branches.

The patient was then admitted as an in-patient and treated with sodium penicillin 1 million units b.i.d. for 3 days owing to the chance of complications. The patient remained unaffected, however, and was now submitted to tomography of the mediastinum and bronchography. Tomography (Fig. 1) revealed an about 3 cm long diverticulum surrounded by cartilaginous rings, while bronchography (Fig. 2) showed the diverticulum to have no branches. Normal bronchial markings in the upper lobe were seen at the same time.

The patient has since been controlled at the Ear Clinic and treated with cough medicine, having so far refused further intervention.

The case history was typical in that the only symptom was an uncharacteristic cough due to irritation, without other complaints and without the



Fig 1

general state being affected Moreover it is characteristic that the evagination was overlooked at the first bronchoscopy This fact will be further discussed below

Occurrence of a tracheal diverticulum is though not a rare exception a fairly unusual clinical finding Most often the diagnosis is made only accidentally after death Chiari (1889) described five cases in detail all found on post mortem examination The earliest description is due to Sandifort (cit by Chiari 1889) in 1785

The phenomenon is also known to have been diagnosed radiographically (Schinz 1951 among others) but it was the development of the bronchoscopic technique which caused it to be diagnosable clinically together with the other tracheal deformities The diverticulum belongs to the so called evaginations (Jordan 1939) It is presumably due either to an abnormally high situated division of the primary lung bud or to a double lung bud (Bremder, 1932)

If this extra lung bud develops completely, the result will be a proper bronchus with branches and lung tissue a so called tracheal secondary lung (Schulte Brinkmann 1961) It may here be a question of an accessory tracheal bronchus i e with simultaneous normal branching of the proper upper lobe bronchus or more often of an abnormal branching off of one of the segmental or subsegmental bronchi of the upper lobe

In such cases bronchographic examination will show lung tissue marking by filling of the abnormal bronchus

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Occurrence of a tracheal diverticulum is, though not a rare exception, a fairly unusual clinical finding. Most often the diagnosis is made only accidentally after death. Chiari (1889) described five cases in detail, all found on post mortem examination. The earliest description is due to Sandifort (cit. by Chiari 1889) in 1785.

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In such cases bronchographic examination will show lung tissue marking by filling of the abnormal bronchus.



Fig. 2

If the development of the evagination stops at an earlier stage, cysts, tracheoceles, or diverticula will occur, dependent on the communication with the trachea.

Bremer (1932) examined 80 five- to eight-week old embryos and found among these three cases of primordial diverticulum. Bremer concludes that the majority of such diverticula remain rudimentary, the defect being much rarer among adults.

Franchel (cit. by Schulte-Brinkmann, 1961), in a series submitted to bronchoscopy, found evagination in 2 per mille of the cases. The patients were selected, however, having respiratory symptoms.

In the typical cases the evaginations proceed from the right lateral wall of the trachea, 2–4 cm from the bifurcation. Most writers claim that such evaginations never occur in the left wall, except in cases of situs inversus (Chiari, 1889; Schulte-Brinkmann, 1961; Henke, 1928). The defect is most frequent among males (Henke, 1928).

The symptoms are few and quite uncharacteristic. They consist in cough with or without expectoration. 14 out of 38 patients with tracheal bronchus collected from the literature (Schulte-Brinkmann, 1961) had no symptoms whatever. The same writer also points out that the evaginations are often overlooked on the first bronchoscopy. This is probably due to the existence of the defect being unknown to the examiner. The tracheal walls are there-

fore not sufficiently closely inspected but the examiner confines himself to looking down the trachea during the passage of the bronchoscope The walls will here be seen to be approximately tangential Factors that also come into play are the direction in which the oblique cut of the end of the bronchoscope is turned and the corner of the mouth through which the bronchoscope is introduced

The diagnosis can hardly be made radiographically on the basis of an ordinary thorax film at least not if an evagination is not suspected Bronchography as well as tomography on the other hand can establish the diagnosis and bronchography even the differential diagnosis between diverticulum and tracheal bronchus with attending lung tissue In addition to the lung marking in the latter cases the direction of the evagination will also give information A diverticulum is usually fairly short and points downwards whereas a tracheal bronchus most often runs a more horizontal or a descending convex course Differentiation is impossible on the basis of an ordinary clinical examination the symptoms being far too vague Bronchoscopically and bronchographically there is however a chance of confusion with other forms of diverticulum in the trachea

As in the oesophagus acquired diverticula such as pulsion and traction diverticula may also occur in the trachea The former have been described particularly by Rokitansky (Denker & Kahler 1928) They develop in chronic catarrhal states with degeneration of the tracheal walls The posterior wall is the most frequent site of such The pulsion diverticula are often multiple and never contain cartilage in the wall

The traction diverticula are seen close to the bifurcation They manifest themselves radiographically (Schinz 1951) as small tent shaped bulgings of the tracheal wall Their development is as a rule related to affections of the mediastinal lymph glands

The differential diagnosis of these diverticula from the congenital will hardly cause any difficulty because as stated the latter proceed from the right wall 2 4 cm above the bifurcation and their walls contain cartilage

Bronchography will as mentioned above distinguish the accessory and aberrant bronchi from the diverticula while bronchoscopy and the presence in some instances of a soft air filled intumescence inferiorly on the neck will disclose the tracheocele (Denker & Kahler 1928) The tracheal cysts do not communicate with the trachea and therefore cannot be confounded with diverticula The tracheo oesophageal fistulae are characterised by a much severer symptomatology Diverticula may be complicated in the first instance by infection In the case under review the mucous membrane was red and irritated Presumably a subactue catarrhal state was present which maintained the cough

Such complicating affections as bronchiectasis and emphysema are likewise claimed to be common (Schulte Brinkmann 1961) whereas neoplasms are believed to be rarer findings Schulte Brinkmann (1961) however saw one patient with carcinoma among five own cases of tracheal bronchus On

the other hand, by reviewing the literature he found among 33 cases only one with complicating adenoma and none with malignant tumour.

Tracheal diverticula will probably require no treatment in the majority of the cases. The symptoms are few and mild and the risk of malignant development not particularly great. Most diverticula are doubtless completely symptom free and are only diagnosed accidentally. In the cases of persistent and pronounced symptoms thoracosurgical intervention may be contemplated.

ZUSAMMENFASSUNG

Ein Fall von angeborenem Divertikel in der Trachea wird berichtet. Die Entwicklung und Diagnose werden diskutiert.

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MYOBLASTOMA OF THE LARYNX

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Myoblastoma of the larynx is a benign, rare tumour Previously, only 32 cases have been described An account is given here of a 9 year-old boy with a myoblastoma of the left half of the larynx, where the only symptom was slight hoarseness By means of indirect laryngoscopy an elevation of the left arytenoid region was visible together with a reduced mobility of the left vocal cord An attempt was made to excise the tumour through laryngofissure, but, on account of the tumorous remnants and continued constriction of the larynx, total laryngectomy had to be performed Macroscopically the tumour was radically excised, but histologic investigations showed that tumorous stripes are present in one of the edges towards the oesophagus Two years after the operation the boy is in good condition and no increase in the tumour has been observed

Myoblastoma of the larynx is regarded as a comparatively rare tumour Despite this during 1962 with only short intervals new cases were reported by Lyons Haindel & Blatt (1962) (5 cases) and by Ward & Oshiro (1962) (1 case) The disease was first described in 1926 by Abrikosoff and up to 1962 26 cases in the larynx had been reported (Balshi 1960, Walter 1960, Beckhuis 1960) and these 6 cases more make totally 32 cases

Histologically the tumour is benign but may develop without a capsule and even grow infiltratively (Frenckner 1938 Ringertz, 1942) A few cases of malignant myoblastoma though not of the larynx, have been described, but it is a question whether these tumours were of the Abrikosoff type (Hunter & Dewar 1960 Gaby Duperrat & Lecochard, 1962) In most cases the usual benign myoblastoma occur in patients between the ages of 30–40 years The youngest case reported is that of a 9 year old boy (MacNaughtan & Fraser 1954) The majority of the laryngeal myoblastomas are situated on one vocal cord and are small, white or greyish white, often polypous sharply demarcated but without evident capsule Hyperplasia of the mucous membrane may frequently be seen around the tumour The symptoms are often slight such as mild hoarseness or cough in a few cases these are more pronounced such as stridor

The usual method of treating the small tumours on the vocal cords is extirpation by direct laryngoscopy In cases where this was the only operative measure recurrence took place in 1 case only In some cases however, it

was necessary to perform a laryngofissure partly in order to establish the diagnosis partly in order to excise the infiltratively growing tumour completely *Out of the 32 cases published hitherto* laryngofissure with excision was performed in 6 cases with good results and without recurrence In 1 case hemilaryngectomy was performed at the same time In 1 case that of the 9 year old boy previously mentioned total laryngectomy was necessary A somewhat more detailed account of this case may be justified since it was similar in several respects to our case Symptoms of mild hoarseness had persisted for two years and slight stridor gradually developed A biopsy by direct laryngoscopy was made from the granular mucosa of the interarytenoid region *Microscopic examination revealed nonspecific granulomatous lesions* One year later the lesion has progressed downward in the trachea and a histological examination now showed the picture of myoblastoma Half a year *later laryngofissure was performed with excision without it being possible* to excise the tumour radically Increasing hoarseness and stridor made it necessary to perform tracheotomy after another six months Irradiation was given without effect Subsequently teleradium was tried but the tumour continued to grow and 3½ years after the presence of myoblastoma had been established total laryngectomy had to be performed (the boy was then 13) Two years after the operation the patient was in good condition

Case Report

A 9 year old boy was taken to a children's hospital in Stockholm on *account of headache Left sided maxillary sinusitis was diagnosed* This was not cured by the usual conventional treatment Consequently the patient was referred to the outpatient department for Ear Nose and Throat diseases at Sodersjukhuset *On rinsing the maxilla only an insignificant amount of* mucous was obtained A routine examination of the larynx showed the left vocal cord to move less freely than the right A certain elevation and swelling of the arytenoid region on the left side with a small pale excrescence was noted Only after questioning the patient's mother did she recall that the boy had been hoarse during the last few months The patient was admitted to the Ear Nose and Throat Department of Sodersjukhuset on 9 January 1961 First an endonasal trepanation was performed in the left maxillary sinus with biopsy from the mucosa The histological examination showed the picture of chronic sinusitis Pulmonary X ray was negative whereas X ray of larynx including planigraphy showed that as well the false vocal cord as the true vocal cord on the left side were swollen The swelling extended for about 1 cm down into the subglottic space The medial border of the swelling was situated a few mm to the right of the median line and the sinus of Morgagni was not visible on the left side Nor could any mobility of the soft parts be observed on this side The soft parts on the right side appeared to move and no appreciable swelling however was visible (Figs 1 and 2)

Laboratory examinations showed normal blood values The electrophoresis



Fig. 1. Tomography showing the swelling of the left side.

was without major pathological features. On 18 January direct laryngoscopy was performed. The arytenoid region was swollen and the recessus piriformis somewhat constricted. The left vocal cord remained stationary whereas the right moved normally. The left false vocal cord was swollen and in the left sinus of Morgagni a relatively pale excrescense the size of a grain of rice, was visible. It was taken for histological examination. The histologic examination revealed, as the main lesion, the growth of a tumour which exhibited the characteristic picture of granular cell myoblastoma. Thus the tumour was built up of cells, the cytoplasm of which was finely granulated and slightly picrinophilic. The tumour cells did not display atypia and mitosis was not observed. The tumour was not demarcated by a capsule.

In view of the pathological findings laryngofissure after tracheotomy was performed in an attempt to excise the tumour radically on 14 February. Already before the thyreoid cartilage was divided, the left half of the larynx appeared to be somewhat firmer than the right. The interior of the larynx on the right side appeared normal, whereas on the left side the tumour was palpated as a firm infiltrate with some small excrescences in the sinus of Morgagni. The tumour grew deep in the soft parts and infiltrated the perichondrium. The thin layer of the posterior half of the thyroid cartilage and of the left frontal part of the cricoid plate were removed together with the tumour. The region of the arytenoid cartilage appeared to be entirely infiltrated and, on this account, the whole left arytenoid region was removed extending somewhat over the median line of the anterior soft parts, in order to reach healthy tissue. Clear muscle fibres were then visible in the dorsal wall towards the oesophagus and the larynx thus remained here without cartilage. During the operation there was only slight bleeding, which was

was necessary to perform a laryngofissure, partly in order to establish the diagnosis, partly in order to excise the infiltratively growing tumour completely. Out of the 32 cases published hitherto, laryngofissure with excision was *performed in 6 cases with good results* and without recurrence. In 1 case hemilaryngectomy was performed at the same time. In 1 case, that of the 9 year old boy previously mentioned, total laryngectomy was necessary. A somewhat more detailed account of this case may be justified, since it was similar in several respects to our case. Symptoms of mild hoarseness had persisted for two years and slight stridor gradually developed. A biopsy by direct laryngoscopy was made from the granular mucosa of the interarytenoid region. Microscopic examination revealed nonspecific granulomatous lesions. One year later the lesion has progressed downward in the trachea and a *histological examination now showed the picture of myoblastoma. Half a* year later laryngofissure was performed *with excision without it being pos*sible to excise the tumour radically. Increasing hoarseness and stridor made it necessary to perform tracheotomy after another six months. Irradiation was given without effect. Subsequently teleradium was tried, but the tumour continued to grow, and 3½ years after the presence of myoblastoma had been established total laryngectomy had to be performed (the boy was then 13). Two years after the operation the patient was in good condition.

Case Report

A 9 year old boy was taken to a children's hospital in Stockholm on account of headache. Left sided maxillary sinuitis was diagnosed. This was not cured by the usual conventional treatment. Consequently the patient was referred to the outpatient department for Ear, Nose and Throat diseases at Sodersjukhuset. On rinsing the maxilla only an insignificant amount of *mucous was obtained. A routine examination of the larynx showed the left* vocal cord to move less freely than the right. A certain elevation and swelling of the arytenoid region on the left side with a small pale excrescence was noted. Only after questioning the patient's mother did she recall that the boy had been hoarse during the last few months. The patient was admitted to the Ear, Nose and Throat Department of Sodersjukhuset on 9 January 1961. First an endonasal trepanation was performed in the left maxillary sinus with *biopsy from the mucosa. The histological examination* showed the picture of chronic sinuitis. Pulmonary X-ray was negative, whereas X-ray of larynx, including planigraphy, showed that as well the false vocal cord as the true vocal cord on the left side were swollen. The swelling extended for about 1 cm down into the subglottic space. The medial border of the swelling was situated a few mm *to the right of the median line, and the sinus* of Morgagni was not visible on the left side. Nor could any mobility of the *soft parts* be observed on this side. The soft parts on the right side appeared to move and no appreciable swelling, however, was visible (Figs. 1 and 2).

Laboratory examinations showed normal blood values. The electrophoresis

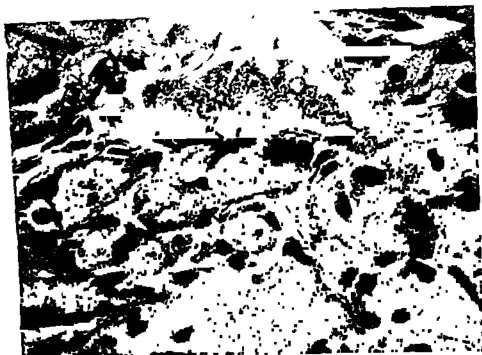


Fig. 3. Details of myoblastoma. The granular cells are readily visible as well as the absence of polymorphism. Magnification approximately ×600.

was observed neither on the back of the larynx nor when inspecting the mucosa of the recessus piriformis. Consequently, the larynx was extirpated in the usual way, and the trachea stricked forward to the skin. Histological examination showed a massive growth of myoblastoma, infiltrating the left vocal cord. Now, as previously, the tumour did not display any actual histological signs of malignancy in the form of atypia, polymorphia or mitosis. On the other hand the tumour was now, as it had been previously, not sharply demarcated with regard to its surroundings. Tumorous tissue was observed to infiltrate the laryngeal surroundings, connective tissue and muscles. Growth of the myoblastoma was revealed in the left resection edge to the oesophagus, but the resection edges lateral to the thyroidal cartilage and arytenoid region were free from tumour.

Post-operative treatment proceeded without any complications. During the first 10 days the patient was fed by means of a stomach tube, subsequently, he was able to swallow freely. The tracheostoma healed well, although at the beginning a tendency to stricture had been noted. A radiogram of the hypopharynx three weeks after the operation showed that even thick contrast medium could pass without difficulty. Despite the fact that the tumour had not been radically excised, radiotherapy was not applied. Already two weeks after the operation speech training was begun.



Fig. 2. Larynx and hypopharynx from side showing swelling of hypopharynx.

easily stanched. The histological examination showed a typical picture of *myoblastoma without capsule and growing into all of the resection edges*.

The boy's general condition was good after the operation, and during the first postoperative weeks he was fed through a stomach tube. Since he was unable to swallow properly, the tube had to remain in place for three weeks. Subsequently, he swallowed quite well, even though afterwards he also frequently swallowed in the wrong way. The tracheostoma could not be closed as the airpassage through the larynx was too narrow. The boy was able to say only a few words at a time and then with a very hoarse voice, inspiration through the larynx was almost entirely abolished. The tracheostoma itself showed also a pronounced tendency to granulation.

For a period of over three months unsuccessful attempts were made to decannulate the boy. If anything, the airpassage through the larynx appeared to be more and more difficult. Moreover, since the tumour had not been radically removed, total laryngectomy was considered to be warranted despite the fact that the patient was only 9 years old. Laryngectomy was performed on 23 May 1961, 4 months after the myoblastoma had been diagnosed.

The region around the left superior cornu is somewhat infiltrated and the perichondrium is more firmly attached to this side than to the right side and the back of the thyroid cartilage. Macroscopically, nothing worthy of note

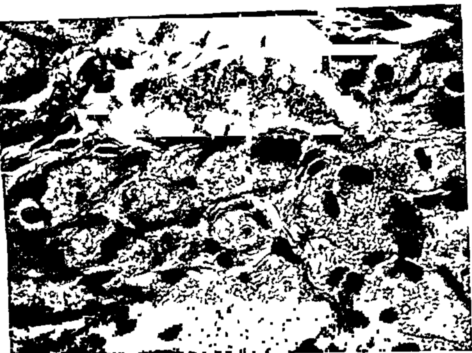


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The further course was very satisfactory. The last X-ray of the oesophagus which was taken not fully two years after operation[1] did not show any signs of infiltration. The tracheal cannula was only used at nights. Since his operation the boy has been regularly controlled and indirect laryngoscopy revealed a pale, soft hypopharyngeal mucous membrane, possibly slightly more rigid on the left than on the right side. The boy's general condition is excellent and he can eat all food without any difficulty. The scars on his neck are slightly firm and tight but no adenitis are palpable. The boy is attending school and doing well.

DISCUSSION

Previously only one case of myoblastoma of the larynx has been described where it was necessary to perform laryngectomy. The previous case like the present one was that of a young boy. With regard to our patient the major operation proved necessary for several reasons: the airpassages via the larynx became increasingly difficult, swallowing often occurred the wrong way with the risk of aspiration and the tumour was not radically excised. On account of the way in which the myoblastoma grows and despite the fact that the tumour is benign the same major surgical measures as those required for malignant laryngeal tumours may be necessary. In view of the benign character of the tumour prognosis must be regarded as good. In the case in question remnants of tumour tissue are still present in the direction of the left border of the oesophagus. Therefore there is a risk that it will infiltrate around the hypopharynx and thus gave rise to a stricture of the oesophagus. Radiotherapy was not applied in this case since the tumours are insensitive to irradiation. Furthermore in a few cases in the literature radiotherapy has been used. No beneficial effect has, however, been noted.

ZUSAMMENFASSUNG

Ein im Larynx gelegenes Myoblastom ist ein gutartiger, doch seltener Tumor. Es sind nur 32 Fälle in früheren Publikationen beschrieben worden. In dem vorliegenden Artikel wird über ein Myoblastom in der linken Larynxhälfte bei einem 9jährigen Jungen berichtet. Das einzige Symptom war eine leichte Heiserkeit. Bei der indirekten Laryngoskopie sah man sowohl eine Auftreibung der linken Aryregion als auch eine Einschränkung der Beweglichkeit des linken Stimmbandes. Mit Hilfe einer Laryngofissur versuchte man zuerst eine Exzision des Tumors, doch musste auf Grund von Tumorresten und bestehender Verengung des Larynx eine totale Laryngektomie gemacht werden. Der Tumor wurde makroskopisch radikal exzidiert, doch die histologische Untersuchung zeigte, dass in dem gegen den Oesophagus gelegenen Schnittrande Tumorreste vorhanden waren. Nicht ganz 2 Jahre nach der Operation befindet sich der Patient in einem guten Allgemeinzustand und eine Vergrösserung des Tumors konnte nicht beobachtet werden.

[1] New X-ray examination (April 1964, i.e. 3 years after operation) equally satisfactory.

ZUM KNOCHENLEITUNGSHÖREN VON IMPULSEN

Physikalische Messungen der Ausbreitungsgeschwindigkeit

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Die Angaben des Schrifttums zur Ausbreitungsgeschwindigkeit von Knochenschall im menschlichen Schädel gehen auseinander. Sie reichen von 100–300 m/sec (Franke, Zwislocki) bis 3000 m/sec (Allen & Fernandez). — Die Abtastung der Schwingungen des von einzelnen Knochenschall-Impulsen angeregten Schädels mit einem beschleunigungsempfindlichen Wandler ohne fremden Bezugspunkt ergab, daß sich sowohl der Kopf des Lebenden als auch das Schädelskelett wie ein anisotropes Medium verhält. An verschiedenen Orten wurden verschiedene Ausbreitungsgeschwindigkeiten gemessen. Auf der Kalotte am niedrigsten (um 500 m/sec), *nahmen* sie zur Schädelbasis hin zu (bis 3000 m/sec). Für den Weg *zwischen beiden* Felsenbeinen benötigten die Impulse etwa 100–200 µsec. Die erste Auslenkung des Beschleunigungsempfängers hatte unabhängig vom Ort stets die gleiche Phase. Demnach riefen diese Impulse nicht Translationsbewegungen des Schädelganzen hervor, sondern transversale Wellen auf seiner *Oberfläche*.

Die Theorie des Knochenleitungshörens kennt die allseitige *Kompression der* knöchernen Labyrinthschale und Trägheitsschwingungen der *Innen*ohrflüssigkeit als wirksame *Anregung des* Cortischen Organes beim Hören von Knochenschall. *Beide* Kompression und Massenträgheit kommen frequenzabhängig *ins Spiel*, wie das *umfangreiche* Schrifttum ausweist (vor allem Barany 1938, v. Békésy 1960, Ranke 1953, Kirikae 1959). In neuerer Zeit wurde dem *Kompressionsfaktor* die *wesentlichere* Rolle zugesprochen (Allen & Fernandez 1960, Huizing 1960, Tonndorf 1963), obwohl damit nicht der Einwand geklärt wurde, *daß* nach Ohroperationen mit Schaffung eines zusätzlichen Labyrinthfensters, also mit Verminderung der Kompression im Innenohr, *das Knochenleitungsgehör* ungestört bleibt oder sogar verbessert wird (McConnel & Carhart 1952, Ranke 1952, Meyer zum Gottesberge 1958, Schmitt, *Kreulle & Wullstein* 1961). Von Goodhill *et al* (1954), Kirikae (1959) und Tonndorf (1952) ist ein beträchtliches Restgehör nach schallhartem Verschluß der beiden Labyrinthfenster elektrophysiologisch (Cochlear M [illegible] satz zu anderen Untersucher [illegible] Verschluß des runden Fenste [illegible] 56). Tonndorf (19[illegible]) hat z [illegible] eine interessante Lösung, eine Torsion der

METHODIK

Als Knochenleitungs-Prüfschall wurden einzelne Rechteckimpulse verschiedener Impulsdauer und verschiedener Intensität benutzt, die über einen Leistungsverstärker einem Knochenleitungs-Telefon (Jaquet, Basel) mit einer ringförmigen Aufsatzfläche von 11 mm Durchmesser zugeführt wurden. Das Knochenleitungstelefon wurde auf dem Kopf des Lebenden mit einem federnden Klemmbügel, auf dem Schädelknochen-Präparat mit Uhu hart festklebend angebracht. Zur Aufnahme des Knochenschalles diente ein Beschleunigungsempfänger ohne fremden Bezugspunkt mit einer runden Aufsatzfläche von 27 mm Durchmesser. Er wurde am Lebenden mit einem Gummiband befestigt, am Schädel mit Uhu hart fest aufgeklebt. In Zusatzversuchen wurde die Aufsatzfläche durch Anlöten eines 5 mm langen Stiftes von 2 mm Durchmesser verkleinert, um eine punktförmige Abtastung auszuführen. Sowohl das Knochenleitungs-Telefon wie der Beschleunigungsempfänger (Rohde & Schwarz, München) wurden mit verschiedenen statischen Auflagedrucken angekoppelt.

Zur Messung der Zeitdifferenzen wurde ein Doppelstrahl-Oszilloskop (Tektronix 502) benutzt. An die Vertikalablenkung des oberen Kathodenstrahles wurde der Rechteckimpuls, an die des unteren Strahles die Ausgangsspannung des mechano-elektrischen Wandlers geschlossen. Gemessen wurde die Zeit zwischen Impulsbeginn (oberer Strahl) und der ersten Auslenkung des beschleunigungsempfindlichen Wandlers aus seiner Nullage (unterer Strahl).

Die gerätbedingte konstante Zeitdifferenz beim direkten Aufsetzen des Knochenleitungs-Telefons auf den Beschleunigungsempfänger betrug 0,029 msec und wurde bei der Auswertung jeweils subtrahiert. Für jeden im nächsten Abschnitt näher bezeichneten Meßpunkt wurden jeweils 3 Aufnahmen mit jeweils 3 Ablenkgeschwindigkeiten (9 Aufnahmen) fotografiert, so daß für die Reproduzierbarkeit hohe Gewähr gegeben war.

Mit dieser Versuchsanordnung konnten lediglich senkrecht zur Schädeloberfläche verlaufende Schwingungen registriert werden, da der Beschleunigungsempfänger nur empfindlich war für zu seiner Aufsatzfläche vertikale Auslenkungen. Als Versuchspersonen dienten 5 normalhörige jüngere Klinikangehörige. Darüber hinaus wurde ein Knochenschädel untersucht, dessen Kalotte an der üblichen Säge-Schnittfläche durch Klebstoff fest mit der Schädelbasis verbunden war. Die Meßpunkte wurden einheitlich gewählt. Der Fehler Δv der Geschwindigkeit wurde über das totale Differential aus den Fehlern der Wegmessung (Δs) und der Zeitmessung (Δt) bestimmt:

$$\frac{\Delta v}{v} = \frac{\Delta s}{s} + \frac{\Delta t}{t}$$

Dabei wurde für Δs der Wert 0,5 cm und für Δt der Wert 0,01 msec zugrunde gelegt.

knöchernen Schneckentreppen im Schallrhythmus, herangezogen und diese Möglichkeit in Modellversuchen dargestellt

Kompressionswellen eilen nach der herrschenden Auffassung so rasch durch den Schädelknochen — 1000 bis 3000 m/sec —, daß sie ein Labyrinth so gut wie gleichzeitig von allen Seiten erreichen, und daß auch beide Innenohren praktisch gleichzeitig angeregt werden[1] Legt man mit Allen & Fernandez (1960) die Ausbreitungsgeschwindigkeit in Elfenbein von 3000 m/sec zugrunde, errechnet sich aus dem etwa 7 cm langen Weg von einem Labyrinth zum anderen über die Schädelbasis eine interaurale Zeitdifferenz von 23 μsec Das ist weniger als normalerweise subjektiv wahrnehmbar Selbst, wenn man die größere Entfernung über das Schädeldach (z B. 34 cm) in Rechnung stellt, ergibt sich ein sog delta t von höchstens 113 μsec Auch das fällt in den Bereich der binauralen Fusion und entspricht noch dem unteren Grenzbereich des Richtungshörens, keinesfalls der Zeitdifferenz beim Lateralisieren von Luftschall in 90° horizontal, d h aus reinseitlicher Richtung Bedenkt man, daß es eine wesentliche Schalldämmung zwischen beiden Ohren für Knochenschall nicht gibt (u a. Barany, 1938), würde außer delta t auch der andere Reizparameter des Richtungshörens fehlen, delta i, die interaurale Intensitätsdifferenz Gibt es demnach kein Richtungshören über Knochenleitung?

Der Erweis stereofonen Hörens mit den binauralen Knochenleitungs-Hörhilfen und die Empfindung binauraler Zeitdifferenzen im Experiment (Wigand, 1962) stehen diesen Erwägungen jedoch gegenüber Letztere legte Ausbreitungsgeschwindigkeiten des Knochenschalles zwischen 500 und 833 m/sec nahe Nun wurden die Erscheinungen des Knochenleitungshörens fast ausschließlich mit Stimmgabeln oder reinen Tönen untersucht Nur v Békésy (1948) stellte im Laufe seiner klassischen Untersuchungen des Knochenleitungshörens eine Ausbreitungsgeschwindigkeit von Knochenschall-*Impulsen* fest, nämlich 570 m/sec Dazu bediente er sich des Knackes, der beim Zusammenklappen der beiden Zahnreihen entsteht Gemessen wurde das Eintreffen der ersten Wellenfront an zwei Schallaufnehmern, die in einigem Abstand auf das Schädeldach aufgesetzt waren Die daraus errechnete Geschwindigkeit der ersten Wellenfront von 570 m/sec würde eine interaurale Zeitdifferenz von maximal 120 μsec bis 600 μsec (7 oder 34 cm Entfernung) gewährleisten Das ist für viele Personen ein knapper Spielraum zur räumlichen Empfindung binauraler Zeitdifferenzen

In v Békésy's (1948) Experiment wurde der Impuls mit den Schneidezähnen erzeugt und konnte die Ableitungsstellen sowohl durch radiäre wie zirkulare Ausbreitung erreichen Die Nachprüfung der Fortpflanzungsgeschwindigkeit von pulsiertem Knochenschall bei Zuführung von außen erschien deshalb interessant Insbesondere waren auch die Verhältnisse am Lebenden mit denen eines Schädelknochen-Präparates zu vergleichen

[1] Nur von Franke (1956) und Zwislocki (1958) wurden niedrigere Ausbreitungsgeschwindigkeiten mitgeteilt 100–300 m/sec bzw 260 m/sec

METHODIK

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[1] Nur von [illegible] (19[illegible]) u. Zwislocki (1958) wurden [illegible] geringere [illegible] mitgeteilt: 10[illegible] 30[illegible] [illegible] sec bzw. [illegible] 60[illegible] m/sec.

METHODIK

Als Knochenleitungs-Prüfschall wurden einzelne Rechteckimpulse verschiedener Impulsdauer und verschiedener Intensität benutzt, die über einen Leistungsverstärker einem Knochenleitungs-Telefon (Jaquet, Basel) mit einer ringförmigen Aufsatzfläche von 11 mm Durchmesser zugeführt wurden. Das Knochenleitungstelefon wurde auf dem Kopf des Lebenden mit einem federnden Klemmbügel, auf dem Schädelknochen-Präparat mit Uhu hart festklebend angebracht. Zur Aufnahme des Knochenschalles diente ein Beschleunigungsempfänger ohne fremden Bezugspunkt mit einer runden Aufsatzfläche von 27 mm Durchmesser. Er wurde am Lebenden mit einem Gummiband befestigt, am Schädel mit Uhu hart fest aufgeklebt. In Zusatzversuchen wurde die Aufsatzfläche durch Anlöten eines 5 mm langen Stiftes von 2 mm Durchmesser verkleinert, um eine punktförmige Abtastung auszuführen. Sowohl das Knochenleitungs-Telefon wie der Beschleunigungsempfänger (Rohde & Schwarz, München) wurden mit verschiedenen statischen Auflagedrucken angekoppelt.

Zur Messung der Zeitdifferenzen wurde ein Doppelstrahl-Oszilloskop (Tektronix 502) benutzt. An die Vertikalablenkung des oberen Kathodenstrahles wurde der Rechteckimpuls, an die des unteren Strahles die Ausgangsspannung des mechano-elektrischen Wandlers geschlossen. Gemessen wurde die Zeit zwischen Impulsbeginn (oberer Strahl) und der ersten Auslenkung des beschleunigungsempfindlichen Wandlers aus seiner Nullage (unterer Strahl).

Die gerätbedingte konstante Zeitdifferenz beim direkten Aufsetzen des Knochenleitungs-Telefons auf den Beschleunigungsempfänger betrug 0,029 msec und wurde bei der Auswertung jeweils subtrahiert. Für jeden im nächsten Abschnitt näher bezeichneten Meßpunkt wurden jeweils 3 Aufnahmen mit jeweils 3 Ablenkgeschwindigkeiten (9 Aufnahmen) fotografiert, so daß für die Reproduzierbarkeit hohe Gewähr gegeben war.

Mit dieser Versuchsanordnung konnten lediglich senkrecht zur Schädeloberfläche verlaufende Schwingungen registriert werden, da der Beschleunigungsempfänger nur empfindlich war für zu seiner Aufsatzfläche vertikale Auslenkungen. Als Versuchspersonen dienten 5 normalhörige jüngere Klinikangehörige. Darüber hinaus wurde ein Knochenschädel untersucht, dessen Kalotte an der üblichen S.-ge-Schnittfläche durch Klebstoff fest mit der Schädelbasis verbunden war. Die Meßpunkte wurden einheitlich gewählt. Der Fehler Δv der Geschwindigkeit wurde über das totale Differential aus den Fehlern der Wegmessung (Δs) und der Zeitmessung (Δt) bestimmt.

$$\frac{\Delta v}{v} = \frac{\Delta s}{s} + \frac{\Delta t}{t}$$

Dabei wurde für Δs der Wert 0,5 cm und für Δt der Wert 0,01 msec zugrunde gelegt.

Fig. 1. Die Schallwellengeschwindigkeit von Knochenschall an verschiedenen Stellen des Schädels. Die Zahlen geben die Geschwindigkeit in Meter pro Sekunde an und gelten für die durch Linien gekennzeichnete Strecke zwischen zwei Meßpunkten. Ausgezogen: Knochenleitungs-Telefon A auf den Scheitel aufgesetzt. Gestrichelt: Knochenleitungs-Telefon B über der Stirnmitte.

ERGEBNISSE

1) *Die gemessenen Zeiten der Knochenschall-Ausbreitung waren unabhängig vom Auflagedruck, von der Impulsdauer und von der Impulsstärke.* In getrennten Versuchsreihen wurden am Lebenden wie am Skelett die Reizparameter verändert. Die Auflagedrucke des Gebers und des Empfängers wurde zwischen 0,1 und ca. 1 kp/cm² variiert. Die beobachteten Abweichungen der Latenzzeiten lagen mit 0,003 msec innerhalb der Fehlergrenze. — Impulsdauern zwischen 0,01 und 1 msec ergaben verschiedene Amplituden, aber unveränderte Latenzzeiten bis zum Eintreffen des Knochenschall-Impulses am Wandler. Erhöhung und Erniedrigung der Impulsspannung am Knochenleitungs-Telefon um den Faktor 10 verursachten keine meßbaren Änderungen der Latenzzeiten für gegebene Entfernungen.

2) *Die Ausbreitungsgeschwindigkeit von Knochenschall im Kopf und im Schädelknochen ist abhängig vom Ort.* Gleichen Strecken entsprechen nicht gleiche Zeiten; der Schädel verhält sich wie ein anisotropes Medium. Die Ausbreitungsgeschwindigkeit erschien über der Kalotte am kleinsten, zur Schädelbasis hin nahm sie grundsätzlich zu. Besonderheiten der Struktur

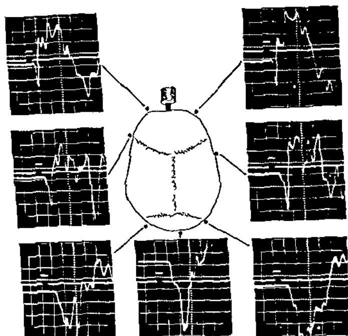


Fig. 2. Oszillogramme eines beschleunigungsempfindlichen Wandlers über verschiedenen Schädelstellen bei Anregung mit einem Knochenschall-Impuls an der Stirne. Die erste steile Auslenkung hat überall die gleiche Phase: eine Auslenkung des Kathodenstrahles nach unten. Zweiter Strahl: Rechteckimpuls

z. B. Knochenwulste, derbe Knochennähte usw. spielten eine Rolle. Für die gleiche Entfernung (7 cm) benötigte der Knochenschall

auf der Schädelkalotte 0,11 msec
auf der Stirne 0,07 msec
an der Schläfe 0,086 msec

Das entspricht Geschwindigkeiten von 635 m/sec (Kalotte) ± 110 m/sec, 875 m/sec (Schläfe) ± 175 m/sec und 1000 m/sec (Stirne) ± 215 m/sec. Beim Abtasten des Knochenschädels mit dem stiftförmigen Ansatz am Beschleunigungsempfänger ergaben sich die Geschwindigkeiten, die in Fig. 1 in ein Schema der Schädeloberfläche eingezeichnet sind.

3) *Die am Kopf des lebenden Menschen und am Schädelskelett gemessenen Geschwindigkeiten der Knochenschall-Ausbreitung* hatten die gleiche Größenordnung und lagen hier zwischen 420 und 3000 m/sec. Tabelle 1 gibt eine Übersicht über die gefundenen Zahlenwerte. Sie enthält die Resultate von 3 Versuchspersonen. Die nicht kompletten Ergebnisse von zwei weiteren Personen bestätigten die Regel, daß die niedrigsten Geschwindigkeiten auf der Höhe des Schädeldaches, die höchsten zur Schädelbasis hin auftraten. Individuelle Unterschiede waren hinsichtlich dieser Tendenz zu vernachlässigen.

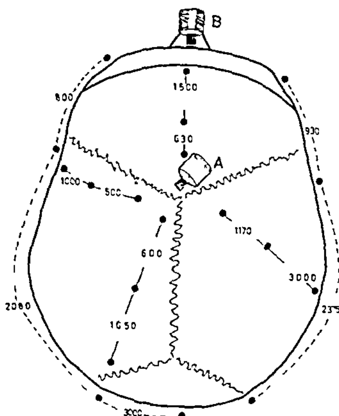


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TABELLE 2. *Die verschiedenen Zeiten, die ein Knochenschall-Impuls braucht, um von den in der linken Spalte aufgeführten Orten zum Beschleunigungs-Empfänger zu gelangen, der hier auf der zur hinteren Schädelgrube gerichteten Fläche des Felsenbeines befestigt war*

Aus den rechts angegebenen Strecken errechnen sich die verschiedenen Geschwindigkeiten der Knochenschall-Ausbreitung

Knochenschall-geber	Geschwindigkeit (m/sec)	Zeit (msec)	Weg (m)
Stirnmitte	770 ± 85	0.15	0.115
Linke Schläfe	810 ± 80	0.16	0.13
Rechte Schläfe	1000 ± 150	0.09	0.09
Linkes Mastoid	875 ± 120	0.12	0.105
Rechtes Mastoid	625 ± 140	0.08	0.05
Scheitel	1190 ± 110	0.16	0.19
Hinterkopf	720 ± 70	0.18	0.13

Beschleunigungsaufnehmer stets am rechten Felsenbein mit Uhu hart befestigt

Beispiel. Daraus geht hervor, daß transversale Knochenschall-Wellen über die Schädeloberfläche laufen. Amplitudenhöhe und -form wurden in diesem Zusammenhang nicht betrachtet.

DISKUSSION

Wir wissen von v. Békésy (1936), daß die Amplitude der Vibration des Schädels linear vom Auflagedruck des Vibrators abhängt und daß insbesondere der Schalldrucktransport durch die lebende Haut für die Frequenzen über 7 kHz stark vom Auflagedruck bestimmt wird. In dieser Untersuchung sollten jedoch nicht Amplituden gemessen und frequenzabhängige Dämpfungen ermittelt, sondern allein die Schallwellengeschwindigkeit beobachtet werden. Sie hängt von der Dichte und dem Elastizitätsmodul bzw. Torsionsmodul des betreffenden Mediums ab. Die evtl. in die Messung eingehenden Hautwellen-Geschwindigkeiten liegen um eine Größenordnung unter den hier registrierten Ausbreitungsgeschwindigkeiten, z. B. wurden von Keidel bis maximal 150 m/sec für die Haut über Knochen angegeben.

Aus den geschilderten Meßergebnissen geht hervor, daß die Ausbreitungsgeschwindigkeit von Knochenschall-Impulsen an den verschiedenen Partien des Schädelskelettes wie des lebenden Kopfes sehr unterschiedlich ist. Sie betrug hier zwischen 420 und 3000 m/sec in Abhängigkeit vom Orte, wobei die kleinsten Geschwindigkeiten auf dem Schädeldach, die höheren zur Schädelbasis hin gefunden wurden.

Die Feststellung derartig hoher Geschwindigkeiten beantwortet nicht die eingangs gestellte Frage, wie das stereofone Knochenleitungs-Hören zu er-

TABELLE 1 *Verschiedene Geschwindigkeiten der Knochenschalleitung an verschiedenen Stellen des Schädels*

Als Weg wurde die kürzeste Verbindungslinie zwischen Knochenschall-Geber und dem beschleunigungsempfindlichen Wandler genommen, der stets auf dem rechten Planum mastoideum befestigt war. Aus den Laufzeiten der Knochenschall-Impulse errechneten sich die durch *Felldruck hervor*gehobenen Geschwindigkeiten. Man erkennt, daß im allgemeinen die Geschwindigkeit vom Scheitel zur Schädelbasis hin zunimmt

Knochenschall-geber auf		VP I	VP II	VP III	Schädel
	V (m/sec)	*1060*	*630*	*830*	*830*
Stirnmitte	± Fehler (m/sec)	90	40	60	80
	Weg (cm)	19	19	20	17
	Zeit (msec)	0.18	0.30	0.24	0.19
	V (m/sec)	*1200*	*1450*	*1230*	*1030*
Re. Stirnhöcker	± Fehler (m/sec)	130	195	135	120
	Weg (cm)	15.5	14.5	16	14
	Zeit (msec)	0.13	0.10	0.13	0.13
	V (m/sec)	*890*	*810*	*530*	*1240*
Li. Stirnhöcker	± Fehler (m/sec)	50	50	25	100
	Weg (cm)	25	21	21	21
	Zeit (msec)	*0.28*	*0.26*	*0.45*	0.17
	V (m/sec)	*880*	*1030*	*1680*	*1310*
Li. Mastoid	± Fehler (m/sec)	70	95	200	140
	Weg (cm)	*18.5*	*17.5*	*18.5*	17
	Zeit (msec)	0.21	0.17	0.11	0.13
	V (m/sec)	*420*	*600*	*610*	*930*
Scheitel	± Fehler (m/sec)	20	10	35	70
	Weg (cm)	18	18	20	18.5
	Zeit (msec)	0.43	0.30	0.33	0.20
	V (m/sec)	*2630*	*1500*	*1430*	*950*
Tub. Occipitale	± Fehler (m/sec)	770	335	280	140
	Weg (cm)	10.5	9	10	9.5
	Zeit (msec)	0.04	0.06	0.07	0.10

Beschleunigungsaufnehmer stets auf dem rechten Planum mastoideum

Stets reproduzierbar war die Beobachtung, daß zur Schädelbasis hin und am Hinterkopf die höchsten Geschwindigkeiten zu beobachten waren, am Scheitel die niedrigsten.

In Tabelle 2 sind die Zahlen für die gemessenen Zeiten, den bis auf 5 mm genau gemessenen Weg und die daraus ermittelten Geschwindigkeiten eines Versuches enthalten, für den der mechano-elektrische Wandler auf der zur hinteren Schädelgrube gerichteten Seite des Felsenbeines in äußerster Labyrinthnähe aufgeklebt war.

4) *Die erste Auslenkung des Beschleunigungsempfängers hatte ohne Rücksicht auf den Ort der Ankopplung stets die gleiche Phase.* Fig. 2 zeigt ein

DRUG EFFECTS ON THE AUDITORY SPEECH DISCRIMINATION MECHANISMS

The action of atropine and scopolamine

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University of Sassari

The influence on hearing discrimination of atropine and scopolamine has been investigated: these drugs are known to depress temporarily the mental performances. The analysis of audiometric results shows that only the intelligibility of low redundancy speech is impaired proportionally to the mental depression. It is concluded that the troubles of sensory message integration caused by atropine and scopolamine leads to a decrease of auditory discrimination and impairs the processes of decoding of the speech message.

The investigation of the effects of drugs on hearing performances may prompt important clues for the solution of some basic problems concerning the neural mechanisms of the auditory discrimination (Bocca & Calearo 1963, Rubin 1963). Particular importance has been attributed to the influence of some central nervous system depressants. The effects of nembuthal, chlorpromazine and meprobamate on the central auditory pathways has been directly checked in the cat with electrophysiological techniques (Antonelli 1963) and in man with psychoacoustic tests (Albano & Antonelli 1963). Evidence has been given that the pharmacological effect is mainly due to a modification of the activation state of the central nervous system and in a lesser degree to a direct action on the auditory pathways (Albano & Antonelli 1963, Antonelli 1963).

In the present study atropine and scopolamine were used in human subjects. The aim of the research was to ascertain

1. whether a direct action of these drugs on auditory system can be demonstrated;
2. whether and to what extent the mental effect of these drugs influences the intelligibility of the speech tests with low redundancy material.

METHODS

Twelve healthy subjects aged between 22 and 65 have been tested. Drugs were administered either orally (4 mg scopolamine, 10 mg atropine) or subcutaneously (1 mg scopolamine, 4 to 5 mg atropine).

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Universitätsklinik für HNO-Kranke, Würzburg,
Deutschland.

Eingegangen am 25. Januar 1964.

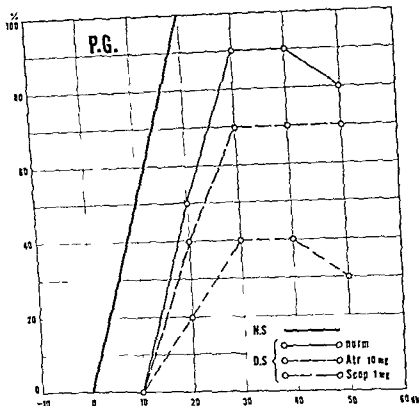


Fig 2 Effect of atropine and scopolamine on distorted speech Same subject as in Fig 1 N.S, Normal speech D.S, distorted speech norm basal conditions Atr 10 mg after 10 mg atropine (single oral dose) Scop 1 mg after 1 mg Scopolamine (by subcutaneous injection)

examiner) The reaction time for visual and acoustic stimuli gave clues as to the influence of drugs on motor and perceptive motor activity of the subject Mean and square deviation of the reaction time to 50 stimuli were computed The choice reaction test was analyzed establishing the average reaction time and the number of faults it gave information as to the stage of evaluation of deliberation, and of decision of voluntary processes of subjects under examination

The explication of some easy proverbs served as an index of reasoning capacity

In order to establish the pharmacological influence on the auditory pathways outside speech integration, the test of interference by a monolateral white noise stimulation on contralateral pure tone adaptation has been investigated (Mantegazzini, Pellegrini & Pestalozza, 1956)

The succession of tests—in basal conditions and following drugs administration—has been varied such as to avoid any possible interference by a process of learning

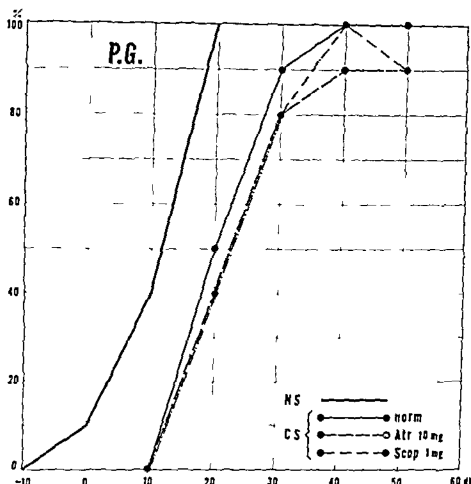


Fig. 1. Effect of atropine and of scopolamine on compressed speech. Subject P. G. N.S. Normal speech. C.S. compressed speech. norm. basal conditions. Atr. 10 mg. after 10 mg atropine (single oral dose). Scop. 1 mg. after 1 mg Scopolamine (by subcutaneous injection).

Both pure tone audiograms and speech tests with normal and low redundancy material (Bocca, Calearo & Cassinari, 1957) have been performed before and after treatment. Since the speech material was limited, we were not allowed to submit all the subjects to each test: thus, interrupted speech test was carried out in 7 subjects after scopolamine and in 8 subjects after atropine; distorted speech in 7 subjects after scopolamine and in 4 after atropine; and compressed speech in 6, both after scopolamine and atropine.

Audiometry started as soon as the effect of drugs had induced clear cut autonomic changes, viz. on pulse rate, blood pressure, salivation, pupillary diameter and visual accommodation power.

Then the subjects underwent a series of psychometric tests: memory tests (11 subjects), time reaction to visual (8 subjects) and acoustic stimuli (10 subjects), tachystoscope (11 subjects), choice reaction test and reasoning test (11 subjects). Memory tests used consisted in memory span for digits (inward and backward), for words (series of 10 couples of words), and in tests of logical memory (repetition of details of a brief report read by the

lel decrease of the performances at the psychometric tests although the auto nomic effects of the drug were present

The psychological tests showing the most significant variations have been the tachystoscope the reaction choice tests and the reaction time while memory tests were less frequently affected

DISCUSSION

The impairment of speech tests with low redundancy material is parti cularly evident for the interrupted and distorted speech and only slight for compressed speech On this subject it should be recalled that previous ex periments showed that the correlation with the I Q is the highest for inter rupted speech and minimal for compressed speech (Calearo & Hahn 1963) The aims of the psychometric analysis were (*a*) to evaluate the mental component of the pharmacological activity of atropine and scopolamine and (*b*) to establish which psychological tests — under drug effect—showed the best correlation with the audiometric ones Scopolamine and—in a consider ably lower degree—atropine at the doses employed impaired all the per formances among them the tachystoscope the tests of choice reaction and of time reaction to sensory stimuli were more frequently and systematically influenced [1] memory and reasoning tests were less affected by the pharma cological activity

A comparative analysis of the drug effect on psychometric and audiometric tests shows thus that they behave similarly the interrupted speech and to a lesser extent the distorted speech showed the same degree of sensitivity as perceptive motor tests Thus it might be concluded that the deficit in speech integration is strictly related to the psycho intellectual impairment

Our results show that scopolamine and atropine do not alter the receptive phase of the auditory integration of speech material i e they do not in fluence the transmission of impulses along the auditory pathways actually pure tone tests and intelligibility of normal speech are not affected On the other hand the pattern of speech intelligibility which ensues from our re sults is very different from the one elicited by barbiturates or by lesions of the auditory pathways (Albano & Antonelli 1963 Antonelli & Cassinari 1963) Even the expressive phase appears to be unmodified as intelligibility of normal speech is quite independent of the pharmacological activity and there is no motor alteration of speech articulation The point of attack of the drugs used appears therefore to be in the perceptive phase where patterns are decodified and their significance is drawn out through comparison with previously memorized models

Thus the impairment of the decoding function in the central nervous system pathological processes is due to a reduction of neuronal population

[1] It should be pointed out that even [illegible]
after scopolamine and atropine This [illegible]
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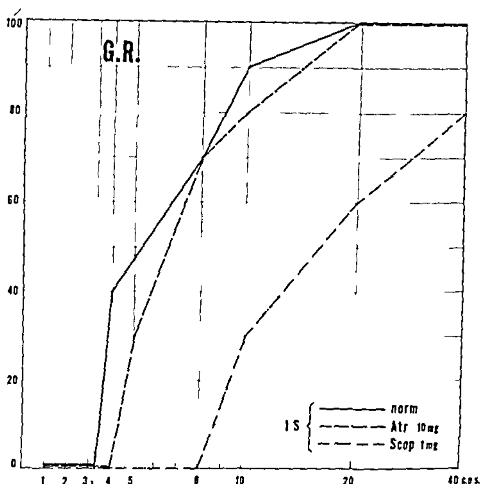


Fig. 3. Effect of atropine and scopolamine on interrupted speech. Subject G. R. IS: interrupted speech; norm: basal conditions; Atr 10 mg: after 10 mg atropine (single oral dose); Scop 1 mg: after 1 mg Scopolamine (by subcutaneous injection).

RESULTS

A comparison with scores obtained under normal conditions shows that scopolamine has impaired the intelligibility of both interrupted and distorted speech in 7 cases out of 7, whereas it has lowered the discrimination of the compressed speech only in 3 subjects out of 6. In no case were the pure tone threshold, the intelligibility of normal speech and the inhibition of contralateral tonal adaptation by stimulation of one ear with white noise affected by drugs. Atropine, on the other hand, has impaired the intelligibility of interrupted speech in *2* cases out of 8, of distorted speech in *2* cases out of 4 and of compressed speech in *1* case out of 6.

As compared with psychometric tests—which will be described in detail elsewhere—whenever scopolamine has damaged audiometric performances the former too were found to be affected. It might even be stated that the audioverbal impairment appears to be proportional to the impairment of the other tests.

Conversely, whenever the pharmacological influence on hearing tests has not been patent, which has l

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Thus the impairment of the *decoding function* in the central nervous system pathological processes is due to a *reduction* of neuronal population

[1] It should be pointed out that even the mean *value of* the time reaction to clicks was increased after scopolamine and atropine *This test* which has been employed *for the detection* of central dysacousis (*Maspétiol*) may therefore be influenced by extra auditory factors

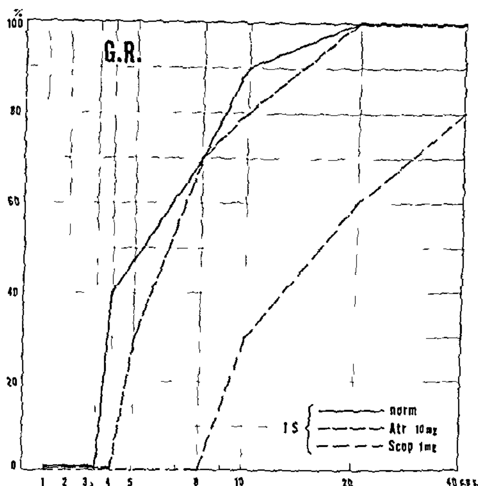


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RESULTS

A comparison with scores obtained under normal conditions shows that scopolamine has impaired the intelligibility of both interrupted and distorted speech in 7 cases out of 7, whereas it has lowered the discrimination of the compressed speech only in 3 subjects out of 6 In no case were the pure tone threshold, the intelligibility of normal speech and the inhibition of contralateral tonal adaptation by stimulation of one ear with white noise affected by drugs Atropine, on the other hand, has impaired the intelligibility of interrupted speech in 2 cases out of 8, of distorted speech in 2 cases out of 4, and of compressed speech in 1 case out of 6

As compared with psychometric tests—which will be described in detail elsewhere—whenever scopolamine has damaged audiometric performances, the former too were found to be affected It might even be stated that the audioverbal impairment appears to be proportional to the impairment of the other tests

Conversely, whenever the pharmacological influence on hearing tests has not been patent, which has happened with atropine, there has been no paral

EMBRYONIC CONNECTIVE TISSUE IN THE TYMPANIC CAVITY OF THE FOETUS AND THE NEWBORN

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After a summary description of the formation of the middle ear cavity and a review of previous studies on the regression of connective tissue in this area, the authors report the results of a pathological study comprising 135 temporal bones from 73 newborn infants The patients represent mainly the developmental stages corresponding to the last 3 foetal months The majority had lived only for a very few days

The middle ear contents consisted of amorphous, loosely fibrillar connective tissue of a fairly uniform degree of differentiation This content varied rather in quantity, a little more than one third of the cavities showing fairly narrow, endosteum like rims of connective tissue and somewhat less than one third a thicker padding which increased in thickness, especially posteriorly The remaining approx 30 % had middle ear cavities in which the connective tissue occupied more than two fifths

Investigation of the site of the connective tissue remnants in the cavity revealed that in about half the cases these remnants were in the postero superior part, while in the other half they were distributed, fairly equally, on the labyrinthine wall close to the oval or the round window and on the floor of the tympanic cavity

In an attempt to contribute to elucidating the significance of the degree of maturity, presentation, duration of life, and respiration to the regression of connective tissue in the middle ear, the results were correlated with the obstetric records In the authors opinion, the first named factor is most important, but energetic respiration is also considered of significance The abnormal presentations in this series are too few to form the basis of deductions regarding the role of presentation and obstetric procedures, if any

The development of the tympanic cavity and adjacent pneumatized spaces has posed many problems in research on embryology In particular, the transformation and regression of the mesenchymal connective tissue from the middle ear does not seem to be fully understood What induces this process and by which factors is it influenced?

As is well known the primordium of the tympanic cavity is laid down in the 3rd foetal week when a fissure shaped pouch from the foregut is invaginated into the not yet completely differentiated mesenchyme In the

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associated with a peripheral alteration of the verbal pattern, conversely the audioverbal effects induced by atropine and scopolamine appear to depend upon a faulty function of decoding centres The intelligibility of the compressed speech emphasizes this difference of pathogenic mechanism: this speech test, which is most influenced by spontaneous and pharmacological (barbiturates) lesions of central auditory pathways, is relatively less affected by atropine and scopolamine The action of these drugs may be attributed to a dysfunction of speech mechanisms which are bilaterally located in the cerebral hemispheres or singly localized in the dominant hemisphere In the latter case, however, the drug activity would most likely elicit disturbances of phasia: therefore the first hypothesis is more probable The function affected by atropine and scopolamine might thus be comprised among the activities of integration of hearing messages belonging to a hypothetic secondary auditory cortical area.

ZUSAMMENFASSUNG

Die Verfasser haben die Hörfunktion nach Lieferung von Atropin und Skopolamin, die bekanntlich die geistige Aktivität hemmen, untersucht Die Analyse der audiometrischen Ergebnisse beweist, dass nur die Artikulationen für die sensibilisierten Sprachtests, abhängig von der geistigen Depression, verändert werden Die Verfasser kommen zum Schluss, dass die von Atropin und Skopolamin geforderten Intelligibilitätsschäden eine Störung der Hördiskrimination verursachen und die Integration der auditorischen Botschaft verschlimmern

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After a summary description of the formation of the middle ear cavity and a review of previous studies on the regression of connective tissue in this area the authors report the results of a pathological study comprising 135 temporal bones from 73 newborn infants. The patients represent mainly the developmental stages corresponding to the last 3 foetal months. The majority had lived only for a very few days.

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primary stage this tissue consists of large uniform stellate cells having nuclei of a fairly high chromatin content and quite ample cytoplasm. The ground substance is amorphous and homogeneous. From approx. the 10th foetal week this primitive tissue shows incipient differentiation in the surroundings of the tympanic cavity primordium. Now the mesenchyme appears to be of a looser structure. The cytoplasm content of the cells increases and their stellate shape grows more irregular. The cells may be more longish and often send wide cytoplasmic processes to the neighbouring cells. This gives the general appearance of a syncytium. The tissue moreover holds an increasing number of amoeboid histiocytes. The ground substance is ample and appears to be a liquid or mucous mass. Around the 16th foetal week this first differentiation of the mesenchyme around the tympanic cavity primordium is so far advanced that the mesenchyme is clearly demarcated from the other primitive tissues. The differentiation is continuous and the gelatinous tissue —which the mesenchyme may now rightly be called—is increasingly predominated by its ground substance. It is getting ever looser and from approx. the 19th foetal week vacuolated.

As might be expected the pouch which is becoming invaginated from the foregut is lined with a stratified columnar epithelium. The tympanic cavity primordium now makes up the lateral part of the pouch and finds its place just within the tympanic membrane. The first ossification zones of the coming middle ear wall are formed in this stage.

From the middle of foetal life the gelatinous tissue seems to start its regression which presumably may take place at a highly varied rate. Moreover inherited individual and acquired factors must be assumed to influence this process.

Previous Investigations

Fabrizi ab Aquapendente was the first worker to mention the mucus content of the foetal middle ear. Morgagni and others also found this mucus and stated that it might be serous or muco-serous in consistency while its colour might range from yellowish to reddish; at times it might be clear or colourless. Tröltsch subscribed to the theory regarding the formation of the tympanic cavity from the foregut but believed that the tympanic cavity was completely filled also during the latter half of foetal life. In Pappenheim's opinion the middle ear mucus was formed by the cells of the vascular gelatinous tissue and he claimed to have demonstrated fibrils in this mucus. Wilde also believed that the mucus content must be due to the highly vascularized tissue in the cavity. Koppen in his dissertation demonstrated that during foetal life and the first weeks of extra-uterine life the middle ear is filled with gelatinous tissue and varying quantities of fluid with desquamated epithelium, fat cells and degradation products. As a rule he found the contents to be greyish yellow, sometimes blood-tinged and serous in the upper part while the lower part was made up of mucous caseous lumps.

Von Tröltsch studied 48 temporal bones from 25 patients who had lived for periods of 17 hours to 1 year. Unlike previous workers, he demonstrated that the middle ear content consisted of vascular embryonic connective tissue (Virchow's mucous tissue) which filled the greater part of the cavity as a padding lined with "beautiful nuclear squamous epithelium". This padding issued mainly from the labyrinthine wall and, according to von Tröltsch, it diminished from birth by shrinkage and desquamation from the surface due to the inflow of air from the Eustachian tube.

von Wreden also assumed that in foetal life the middle ear was filled with primitive connective tissue, but also stated that this padding would disappear or diminish by regression during the first hours of life due to inflow of air through the Eustachian tube at the onset of breathing, crying or sucking. However, he also found remnants of connective tissue in infants who had lived for 12–24 hours and in that case especially in the area of the antrum, on the labyrinthine wall or in the epitympanic recess. He did not find any particular characteristics in the premature infants, but the middle ears of stillborns he found to be filled with connective tissue. This author considered the regression of the connective tissue to be a "regressive metamorphosis", *but did not observe cellular breakdown* or suppuration like von Tröltsch.

Studying 2 stillborn infants and one who had lived for 3 hours, *Zaufal* found the middle ears to show a low mucous membrane with ample liquid substance in the cavity. There was cellular breakdown and pus cells *in the* lumen, so he could not accept von Wreden's theory.

Wendt, investigating the temporal bones of 17 foetuses and 11 newborn infants, found a connective tissue padding on all the walls of the cavity except for the area of the drum. This rim was usually thickest on the labyrinthine wall. In the study of 24 temporal bones from 12 stillborns, this author found 8 bones in which the padding was fairly dominant, while the remaining 16 showed only lower rims of connective tissue. He assumed that the connective tissue was predominant in cases without any energetic breathing during intra- or extrauterine life, but he also attached some importance to the change in circulation at birth, while the foetal and extra-uterine age in themselves were considered of subordinate importance.

During the subsequent years von Wreden's theory found quite a number of adherents. Moldenhauer accepted it with a few reservations, since he assumed that the regression of connective tissue might take place also during foetal life in the event of a diminution of the pronounced hyperaemia in the area. During a short space of time the theory acquired practical significance since the "ear test" was introduced as a diagnostic method in legal autopsies in certain institutes of forensic medicine in Germany (von Hofmann). But soon the sceptics increased in number. Blumenstock, studying macerated stillborns, found completely empty cavities. Kutscharianz believed that the connective tissue regression occurred in the 9th foetal month and that thereafter the cavity held only clear fluid, while pus indicated inflammation. Unlike Kutscharianz, Schmaltz demonstrated highly varied mucous rims in

his temporal bones from newborns, apparently independent of breathing, if any. This made him assume that the presence of amniotic fluid in the middle ear might be due to simple movements of swallowing and that it need not necessarily be accompanied by pulmonary aspiration.

In essential respects Lesser agreed with Schmalz and supplemented his ideas by demonstrating that fluid-filled tympanic cavities were *found chiefly* within the group of stillborn infants who had reached a degree of development corresponding to the 7th foetal month or beyond that. In his opinion the amount of fluid could not be correlated with aspired amniotic fluid, if any, in the lungs. In the tympanic cavities of living infants Lesser did not find air or fluid until the infants had been breathing for several hours, and he did not think there was any parallelism between the quantity of the cavity contents and the length of extrauterine life.

Hnevkovsky assumed that Virchow's mucous tissue regressed from the lumen of the tympanic cavity in the 5th-7th foetal month, after which it was replaced by mucus from the connective tissue and amniotic fluid. He considered diffusion and capillary action to be less important than the entrance of amniotic fluid through the Eustachian tube. Hnevkovsky also demonstrated the entrance of fluid into the tympanic cavity when dead bodies were immersed in water. This definitely did away with the above-mentioned "ear test" as an applicable evidence that an infant had lived after birth. *This author also disagreed with Lesser, as he did not consider that one or* more hours of life were needed before air would flow in.

In the subsequent decades interest centred mainly on the influence of exogenous factors upon the regression of the connective tissue and the significance of the latter to the formation of the tympanic cavity and the pneumatization of the adjacent osseous areas. Aschoff believed that amniotic debris might make its way into the tympanic cavity as early as about the 5th foetal month, but he always found the most pronounced invasion around the time of birth, at which the presence of meconium etc. increased the risk of infection. Incidentally, Aschoff found highly varying configurations of mucous membrane even at early stages of foetal life, and he believed that the vascularity was a more important factor in this respect than the stage of development. In a matter-of-fact way, he stated that the presence of amniotic debris must be considered to have occurred during intrauterine life, if extrauterine breathing or swallowing could be ruled out. Similarly, he explained the presence of air-filled tympanic cavities in dead infants as a consequence of ingress of air in or outside the birth canal. Aschoff felt that ingress of air might in general take place at a highly varying rate and that the length of extrauterine life or the nature of respiration did not afford sufficient basis for deductions regarding the absorption of the connective tissue rim. He considered mucosal changes—e.g. in suffocation haemorrhage—to predispose to infection, which presumably would inhibit the connective tissue regression. However, he did not present details regarding this aspect, just stated that otitis media neonatorum was a regular foreign body otitis.

On the other hand Wittmaack in his pioneer comprehensive monograph dealt with the effect of exogenous factors upon the mucosa and the influence of the various types of mucosa upon the pneumatization of the adjacent bony areas Strangely enough he used the term mucosal constitution In his opinion normal and complete pneumatization of the temporal bone could take place only if the surface layer of the tympanic cavity was normal viz had been spared the actions of the named exogenous factors He set up various abnormal types of mucosa entailing different ultimate stages of pneumatization He distinguished fundamentally between hyperplastic and hypoplastic fibrous mucosa The former was considered to have been produced by the entrance of amniotic debris which may occur from the middle of foetal life This condition he considered to be due to a latent sterile mucus producing infection manifesting itself as subepithelial lymphocytic infiltration vascular dilatation and effusion The connective tissue rim is wide and the myxomatous connective tissue most distinctly visible in the deeper layers Gradually a true process of proliferation takes place and the appearances are characterized by hyperplasia while at the same time the regression of connective tissue is delayed

Wittmaack interpreted the fibrous hypoplastic mucosa as a consequence of bacterial exudative inflammation transforming the connective tissue rim into a thin fairly acellular layer characterized by numerous fibrils The surface layer is made up predominantly of flat cells This condition too leads to reduced pneumatization of the surrounding areas

Like many previous authors Wittmaack was convinced that the *regression* of the connective tissue in the middle ear was induced by the invasion of epithelium from the foregut However he disagreed with previous authors *in considering* the mesenchyme a specially prepared medium determining the cavity formation in the tympanic cavity as well as the pneumatization of the entire temporal bone Wittmaack s ideas were supported by many investigators Steurer studying temporal bones from 100 patients with a highly varied pneumatization found the mucosal appearances to agree with Wittmaack s theories *in* 91 % *However* a number of the workers to be mentioned below were more reserved in their evaluation But all considered it must be admitted even to day that Wittmaack s ideas were original *and highly interesting* and seem to have been a source of inspiration to numerous subsequent studies

Unlike Wittmaack who had attributed the influence of exogenous factors upon the middle ear *mucosa with* such great importance to cavity formation and pneumatization and who had thereby given definite priority to a phenotypic genesis Albrecht advanced a theory which laid the main emphasis upon a genotypic causal relation In his view the general constitution as well as the constitution of the *individual* organs was the main factor governing the mucous membranes pneumatization and the frequency of middle ear infections demonstrating their *familial occurrence* the *predisposition being* presumably transmitted as an inherited character In studies on series of

foetal temporal bones he demonstrated fairly marked individual variants of cavity formation, while the two temporal bones from the same patient nearly always showed *parallelism. In a number of his preparations* Albrecht found deficient cavity formation without any signs of infection. Reversely, he often observed ample cavity formation combined with massive infection. On these grounds he had to oppose to Wittmaack's theories, although he did not explicitly reject them. On the other hand, like Wittmaack, he attributed the ingrowing epithelium with an inducing role and also emphasized the significance of the connective tissue, giving close attention to its degree of differentiation, density and structure. Albrecht interpreted certain thickenings in the cavities as colloidal structures, believing that they might inhibit pneumatization. Moreover, he accepted the theory of Voss concerning the *inhibitory effect of haemorrhages upon pneumatization.*

In collaboration with M. Schwarz, Albrecht investigated a large series of temporal bones and correlated the findings with the constitutional types (pyknic, asthenic and athletic). They felt they could demonstrate that the first type was most often combined with hyperplastic middle ear mucosa, while asthenics generally had fibrous hypoplastic middle ear mucosa. *Per se* the latter type of mucosa was believed to be less reactive, so that susceptibility to infection and capacity for pneumatization were believed to be to some extent correlated.

Meyer, like Marx before him, believed that embryonic otitis and otitis *during infancy were purulent, but that owing to differences in the tendency* to organization their manifestation differed. Meyer considered congenital and constitutional properties to be by far the most important factors in the matter of connective tissue regression.

M. Schwarz conducted, among other things, thorough investigations into the components of the connective tissue at various stages of development. He described the surface layer of the tympanic cavity as a flat cuboidal simple endothelium. This interpretation was based on the study of 101 temporal bones in various stages of development, from the 2nd foetal month and onward. His description of the mesenchyme is in principle in accordance with the classifications of Maximow & Bloom. The earliest preparations showed "embryonic myxomatous connective tissue" with large stellate cells with ample cytoplasm loosely arranged in a syncytial pattern without fibrils. The next type was termed "precollagenous connective tissue" and characterized by stellate cells with a less ample content of cytoplasm, an increasing number of histiocytes and incipient collagenous fibrils. The third type of connective tissue was called "amorphous loose fibrillar", showing narrow spindle-shaped fibroblasts with a number of collagenous fibrils and histiocytes. He could only partially correlate the foreign body content in the tympanic cavity with the occurrence and number of histiocytes, while the nature and quantity of ground substance was independent of the contents of the tympanic cavity. In particular, the number of *collagenous fibrils* appeared to increase in late foetal life. M. Schwarz concluded that ultimately

he structure and regression of the connective tissue must be due to individual actors concerned mainly with the fibroblast, its maturity and ability to form fibrils He tried to classify the connective tissue in his collection of tem poral bones distinguishing between five types of cavity

1 tympanic cavity with a low mucoperiosteal rim of mucous membrane
2 tympanic cavity with cavity formation in the lateral part of the epitym panic recess and a wide rim of connective tissue
3 tympanic cavity in which the medial part of the epitympanic recess like the hypo and meso tympanon showed cavity formation
4 tympanic cavity with a fissure around the head of the stapes
5 tympanic cavity with a fissure along the tympanic membrane reaching to the anterior limb of the stapes

Like most other workers M Schwarz had too few very small embryos to be able to draw definite conclusions concerning the earliest stages of de velopment He found a far reaching agreement between the two temporal bones from the same patient and on the basis of his investigations he was able to demonstrate that stage 4 was the most common one until the 5th foetal month while from the 6th month stage 1 could be reached At birth he considered that the tympanic cavity formation was completed in all es sentials Incidentally, stages 1 and 2 were found in about 80 % of his prepara tions

M Schwarz found amniotic debris in cavities from foetuses older than 5 months and in all preparations from the period around birth He did not think this phenomenon exerted any major inhibition upon the connective tissue metamorphosis In his material the connective tissue remnants were distributed by 43 % in the area above and lateral to the head of the malleus 11 % in the area at the oval window 10 3 % in the vicinity of the round window 9 5 % in the medial part of the epitympanon and 6 1 % at the floor of the tympanic cavity He accepted Wittmaack s views regarding the role of the mucosa in subsequent pneumatization but like Albrecht he felt that inherited and individual factors were far more important than the in fluence of exogenous factors

Singer attributed the formation of cavity to the connective tissue itself, and did not believe that the invading epithelium was concerned with it In his opinion the connective tissue metamorphosis was due to decreasing viscosity dissolution and absorption as well as normal growth in the sur roundings but he also considered exogenous actions e g inflammation to influence the reactive properties of the mesenchyme Incidentally Singer could not confirm Wittmaack s theories by his studies of mucosal types and degrees of pneumatization He also opposed the idea that the hyperplastic mucosa was due to a sterile mucus producing inflammation

In the question regarding the role of the mucous membrane in cavity formation Ruedi s attitude is intermediate between Wittmaack s and Al brecht Schwarz s In his opinion the cavity formation was caused by two

independent factors (1) formation of air cavity and (2) preformation of osseous space *He felt that an individually varied rhythm was initiated by* dissociation unlike the normal associated development In serial sections of temporal bones from a number of infants who had not had aural diseases he found both processes to be present towards the end of the first year of life provided that exogenous noxae did not manifest themselves In the event of infant otitis the pneumatization was inhibited and the process of bone preformation was secondarily affected Ruedi studied 53 temporal bones from age groups ranging from the 5th foetal month to the 10th year of life Like Singer he rejected the role of the epithelium He demonstrated many areas where it was difficult to distinguish the connective tissue from the surface layer However the latter was found to be formed predominantly by a flat cuboidal layer replaced here and there by stratified columnar epithelium Like Albrecht he did not find the cavity formation to be definitely influenced by the common foreign body otitis Anson and Bast have published excellent illustrations of foetal sections and a splendid though rather narrow time table showing the development of the Eustachian tube and the tympanic cavity The metamorphosis of the peritympanic connective tissue into sharply *delimited areas is of particular interest Their contribution is purely* descriptive and thus affords no explanation of or attitude to the genesis of the connective tissue regression

*The previous studies were followed up by H W Schwartz who investiga*ted twins as well as entire family groups in order to elucidate the relationship between the appearances of the middle ear mucosa and the later total pneumatization *He too considered inherited factors of most importance* attaching less significance to exogenous actions

Wilson called for an analysis of the connective tissue content in the middle ear of infants He stressed the special anatomical factors *applying to the Eustachian tube in foetuses and newborns and considered the entrance* of amniotic fluid and infection to be of great importance

Schwarzbart subscribed to the theory that the osseous part of the Eustachian tube belonged developmentally to the mesoderm while its membranocartilaginous part was an entodermal derivative In his comprehensive studies he found a simple smooth cuboidal endothelium like surface layer peripheral to the isthmus of the Eustachian tube From this he concluded that since this layer covered only a narrow rim of connective tissue the cavity was not lined with true mucosa

Present Investigations

The present material comprises 135 temporal bones from 73 newborn infants 65 of whom *had been born in the maternity departments of the University* Hospital while 2 were born in other hospitals one in a private hospital and 5 at home

Four had a birth weight under 1000 g 55 weighed 1000 2500 g 9 from 2500 3500 and 5 more than 3500

Three were stillborn 56 lived for a maximum of 3 days and 13 survived for up to 3 weeks

Four infants were in transverse presentation and in 5 cases version and traction were needed In 4 cases a limb presented and in 9 the breech A total of 11 were delivered by Caesarean section In 4 instances there had been prolapse of the cord in 3 cases intrauterine haemorrhage and in 10 cases the obstetric records mention a suspicion of intrauterine asphyxia

The material includes temporal bones from 2 sets of twins and moreover preparations from 2 infants whose twin siblings had survived

Obviously the infants of the present material belonged to the poor lives The maternity departments of the University Hospital admit a large quota of expectant mothers in whom complications are expected including abnormal presentations maternal diabetes mellitus toxaemia and Rhesus sensitization Moreover a large proportion are admitted on social indications

The temporal bones were removed as soon as possible after death fixed by the method of Wittmaack and decalcified in sodium formate/formic acid by the technique of Kristensen embedded in celloidin and cut into sections of approx 15 μ As a matter of routine every 10th section was picked out and stained with haematoxylin eosin together with specially illustrative sections

Results

Our investigations revealed a highly varied content of connective tissue in the tympanic cavity 27 patients showed only a very narrow rim of connective tissue lining the cavity as an endosteal layer (Fig 1) 13 had a somewhat thicker padding and 11 in addition had connective tissue partially filling the postero superior part of the tympanic cavity In 7 instances between two fifths and three fifths of the cavity was filled (Fig 2) in 11 cases at an estimate four fifths while completely filled tympanic cavities were observed in only 4 cases (Fig 3)

In the great majority of cases the demarcation of the connective tissue from the free cavity was sharp even and in convex and concave waves In cavities where the connective tissue was no longer predominant there were frequently tissue remnants which in the form of strands or bands of irregular formations tied the ossicles to each other or to the walls of the cavity Desquamated connective tissue components were rarely found in the cavities

Comparison of the two temporal bones from the same patient revealed no essential at any rate no fundamental difference in the extent of the connective tissue The same applies to comparison of serial sections from twins

Residual pads of connective tissue were found in about 50 % of the cases posteriorly and superiorly in the tympanic cavity while in the remaining



Fig. 1. Horizontal section of middle ear from a full term infant. Apart from a narrow rim of connective tissue along the wall and a few septa binding the ossicles, the tympanic cavity is air filled. Mag. ×13.

cases these structures were distributed in the following sites: Around the oval window, around the round window, near the Eustachian tube, and on the floor of the cavity.

As already mentioned, the present patients represented mainly the developmental stages corresponding to the last 3 foetal months. In addition there was a small number of full term infants. In accordance with the fairly narrow embryological range, histological examination of the connective tissue showed great uniformity in the differentiation in the various series of sections. The connective tissue consisted largely of an amorphous, loosely fibrillar network with numerous fibroblasts, a number of collagenous fibrils and a somewhat more varied number of histiocytes (Fig. 4). Only a very few cases showed connective tissue which might deserve the designation "precollagenous", and no section contained truly "embryonic myxomatous connective tissue".

More than half the preparations included major or minor vacuoles in connective tissue remnants (Fig. 5). This phenomenon, no doubt interpretable as a stage of the connective tissue regression, was found especially in the presence of fairly large pads of connective tissue. Fusion of several vacuoles had gradually formed major cavities. This was a fairly common finding.

By comparing the birth weight with the connective tissue content of the middle ear cavity, we tried to assess the role of the stage of maturity in the



I ig 2 Mi l lle ear cavity from a premature infant The posterior half is filled with slightly dif ferentiate l connective tissue Mag ×13



I i 3 Mi l lle ear cavity from a premature infant Note the narrow air filled fissure which ex ten ls l ke a continuation of the I ustachian tube to a site behind the tympanic membrane The ren ain ler of the osseous cavity is quite filled with connective tissue remnants Mag ×13

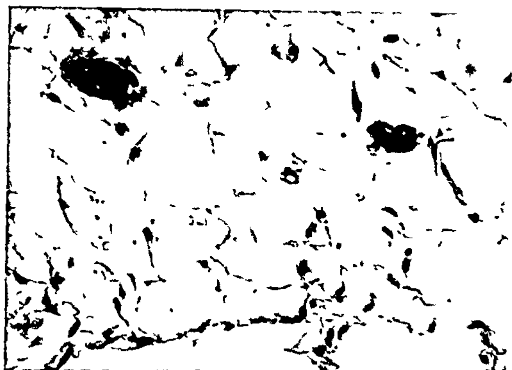


Fig. 4. Connective tissue of low differentiation from the middle ear of a premature infant. Note particularly the irregular tissue structure, the fairly large number of fibroblasts, and the collagenous fibrils. Mag. × 200.

tissue regression. The material includes 4 patients whose birth weight was less than 1000 g. In all 4 the connective tissue filled at least two fifths of the cavity. Among 55 patients having a birth weight between 1000 and 2500 g there were 21, and out of 9 in the weight group 2500–3500 g there were 2 in whom the connective tissue was of this extent. Among 5 patients weighing more than 3500 g at birth none showed the connective tissue to occupy as much as two fifths of the cavity. Of course, the material is not large enough to warrant definite conclusions, but it certainly does indicate that the stage of maturity *per se* influences the regression of the connective tissue in the middle ear.

Investigation of serial sections from the 3 stillborn patients showed uniform, narrow rims of connective tissue in the tympanic cavities. Among 10 patients who had survived for from 0 to 4 hours after birth, 5 showed a connective tissue content occupying more than two fifths of the osseous cavity. Similar findings were made in 9 out of 23 patients who had survived for from 4 to 24 hours, while such a quantity of connective tissue was found in only 8 out of the 37 infants who had lived for more than 24 hours.

These results indicate a probable correlation between survival time and regression of connective tissue in the middle ear.

Isolated assessment of the influence of breathing upon the connective tissue in the middle ear is extremely difficult. While the period during which respiration has been established is approximately identical with the duration



Fig. 5. Incipient vacuolation in the primitive connective tissue from the middle ear of a premature infant. Mag. 64.

of life and is thus easy to determine, the respiratory rate and depth are often so varied in the neonatal period that any evaluation of these factors must often rest on an estimate. The clinical assessment is difficult because of the very short observation period, and moreover autopsy rarely gives essential or supplementary data. In the present group of cases only 8 out of 73 had fully expanded lungs, and with this slight variation we can merely state that the material does not clinically or pathologically afford sufficient basis for a grading. Nevertheless, it may perhaps be of interest to know that in 10 of 35 patients who had cried immediately after birth the subsequent study of temporal bones showed a connective tissue content occupying more than two fifths of the tympanic cavity. In comparison there were 9 patients who never acquired normal breathing, uttering only gasps. Among this group at least 6 showed more than two fifths of the tympanic cavity to be occupied by connective tissue.

Of the 9 breech cases 4 showed more than two fifths of the tympanic cavity to be filled with connective tissue. In two the cavities were even completely filled. The birth weights of these two infants were 1100 and 2050 g and breathing had never been properly established in either case. They lived for only 1 and 5 hours respectively.

Four infants were in transverse presentation and were delivered following version and traction. Two exhibited the above mentioned quantity of connective tissue in the middle ear.

Eleven patients were delivered by Caesarean section and in 3 more than two fifths of the tympanic cavity was filled with connective tissue. It is worth mentioning that the mean birth weight in this group exceeded that in the total series, 4 out of 11 weighing more than 3000 g.

Comments

The present material of temporal bones was derived chiefly from patients who represented a development corresponding to the last 3 foetal months. *The preparations therefore afford no possibility of evaluating the first* stages in the development of the middle ear.

The content of connective tissue in the tympanic cavities proved to be fairly varied despite the relatively narrow embryological range. A little over one third were lined with very narrow endosteum-like rims of connective tissue, while somewhat less than one third had a wider cover which might increase in thickness, especially posteriorly. A total of about 30 % of the serial sections showed middle ear cavities in which the connective tissue made up more than two fifths of the total volume. Only 4 cases had temporal bones in which the connective tissue filled the entire cavity except for the fissure-shaped area just behind the drum, viz. the earliest anlage of the middle ear.

In M. Schwarz's classification of the connective tissue mass in the middle ear 80 % of the serial sections belonged to the above mentioned stages 1 and 2. Our principle of classification may be correlated with M. Schwarz's as his stages correspond approximately to the first two groups of our analysis. These groups comprise about 70 % of all the temporal bones.

Our findings of the sites of connective tissue remnants in the tympanic cavity also correspond approximately to those of M. Schwarz, although we do not feel entitled to quite as rigorous a classification.

As early as about 1870 von Wreden advocated the theory that ingress of air through the Eustachian tube when breathing starts was the cause of the regression of connective tissue in the middle ear. However, subsequent investigations have revealed that this process may take place also without the aid of respiration. And yet, the present results indicate that an increased *lifetime as well as energetic respiration contribute to the regression*, although these factors are not so intimately bound up with each other as to be indistinguishable in their influence.

There has been no previous discussion of the influence of presentation and obstetric procedures, if any, upon the passage of air and amniotic debris through the Eustachian tube of the newborn. Our material includes 11 patients who had been *delivered by* Caesarean section, *and among these* infants 3 showed fairly large amounts of connective tissue in the middle ear despite the fact that all were in a fairly advanced stage of development. Among obstetricians it is an established fact *that infants delivered by* Caesarean section are withheld the normal drainage of the lungs which takes

place during the period of expulsion It must be considered likely therefore, that the passage through the Eustachian tube may be influenced also Some thing like this presumably applies to breech cases In our material 4 of the 9 patients who had presented by the breech showed fairly large quantities of connective tissue in the tympanic cavity

In our opinion infection plays no major role in the fate of the connective tissue in newborn infants while this influence no doubt increases later and as emphasized by Wittmaack presumably affects cavity formation also apart from the tympanic cavity proper

ZUSAMMENFASSUNG

Nach einer kurzgefassten Übersicht betreffs der Bildung der Pauke und über die früheren Arbeiten der Bindegewebsregression im Mittelohr werden die Ergebnisse einer pathologisch anatomischen Untersuchung von 135 Felsenbeinen bei 73 Neuge borenen dargestellt Die Patienten vertreten besonders die Entwicklungsstadien in den letzten Embryonalmonaten

Der Inhalt des Mittelohres bestand aus losem fibrillarem Bindegewebe von ziemlich gleicher Differenzierung Die Menge zeigte sich ziemlich wechselnd, indem 37 % von den Pauken eine ziemlich schmale endost ähnliche Bindegewebsschicht enthielten 33 % hatten besonders hinten ein dickes Wandpolster In den übrigen 30 % der Pauken war mehr als ⅔ der knöchernen Höhlen von Bindegewebe ausge füllt

Eine Untersuchung der Lokalisation der Bindegewebsrückstände im Mittelohr erwies dass diese sich in 50 % der Fälle hinten und oben im Mittelohrraum befanden, und sich sonst einigermassen gleichmässig auf die Labyrinthwand (in der Nähe des runden und ovalen Fensters) und auf den Paukenkeller verteilten

In einem Versuch über die Bedeutung des Maturitätsgrades der Geburtsstellungen der Zeit bis zum Tode des Kindes und der Respiration für die Rückbildung des Bindesgewebes der Pauke beizutragen wurden die Ergebnisse mit den Kranken geschichten verglichen Nach der Auffassung des Verfassers ist der erstgenannte Faktor der wesentlichste aber auch eine energische Respiration scheint von Be deutung zu sein

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VENOUS OBSTRUCTION OF THE COCHLEA BLOOD FLOW AND FUNCTION

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The functional significance of the inferior cochlear vein (vena aqueductus cochleae) is further investigated Occlusion of the inferior cochlear vein resulted in a severe drop in cochlear blood flow and cochlear microphonics After venous occlusion increase of blood flow produced by epinephrine is correlated with an increase of the microphonic response Some general relations between cochlear blood flow, function and oxygen utilization are discussed

Recent experiments indicate that graded increases in blood flow in the vessels of the stria and spiral ligament can be achieved with the administration of pressor agents (Perlman *et al* 1963) However, in the normal animal even a two fold increase in flow velocity so produced does not alter cochlear function *i e* microphonic response to 277 cycles at 90 db On the other hand marked reductions in cochlear (strial) blood flow can be produced by obstructing the venous return from the cochlea This is followed by a severe functional loss as reflected in the microphonic output The anatomical arrangement of the venous system of the cochlea suggests that venous obstruction might play a role in cochlear disease and deafness in man comparable to retinal disease and blindness due to thrombosis of the central retinal vein In man and in the guinea pig the inferior cochlear vein (vena canaliculi cochleae Nabeya 1923 vena aqueductus cochleae Siebenmann 1897) after leaving the basal turn enters a separate minute bony channel adjacent to that of the cochlea aqueduct The late A N Griffith (1961) pointed out that sometimes in the human ear the vein may not go through a bony canaliculus to the inferior petrosal sinus but may course through the submucosa of the middle ear and thus may be exposed to infectious agents and pressure changes in the tympanic cavity

According to Siebenmann (1894) and to Nabeya (1923) the vein carries the major portion of the venous outflow from this part of the inner ear Some of the effects of acute and chronic obstruction of this vein and in the guinea pig have been described (Kimura, Perlman 1956 Perlman 1952) They include severe reductions in blood flow, changes in cell structure and cochlear function

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Preliminary observations with pressor agents indicated that blood flow could be improved in a cochlea with such a compromised circulation. A study of these changes along with changes in microphonic responses was carried out to reveal some additional relations between cochlear blood flow and function.

METHOD

The cardiopulmonary state of the animal is monitored through appropriate electrodes and transducers recording the EKG, EEG, respiratory pressure, carotid pulse pressure and end tidal CO_2 (see Perlman *et al.* 1963). Cochlear function as reflected in the microphonic response to a 277 cycle tone is recorded from differential electrodes in the basal turn and in the third turn of the cochlea.

Moving picture records of blood flow in the vessels of the stria and spiral ligament are taken through the microscope at intervals and subsequently analyzed with a frame counter. In a typical experiment baseline values of cardiorespiratory function and microphonic response are established along with movies of normal blood flow.

Then by lowering and shifting the position of the animal but without disconnecting it from the electrodes or transducers the area of the inferior cochlear vein just after it leaves the cochlea is centered under the operating microscope and the vein is exposed and occluded by drilling away the overlying bone. At this location the venous branch to the internal meatus is probably also interrupted. A properly placed lesion produces severe alteration in cochlear blood flow and microphonic response. If the occlusion is a few millimeters distal to this point, minimal changes in blood flow and function are produced because of good venous return through the collateral vessels.

The animal is then repositioned and recording of cardiopulmonary function, cochlear blood flow, and microphonic response is resumed.

This pathological state is usually sustained without much evidence of further deterioration for 30 minutes or longer. Now epinephrine is administered for 5 minutes at the rate of 0.1 cc/minute and a dose of 5 μg per kg. The resultant changes in carotid pressure, cochlear blood flow and microphonic response were recorded along with the other parameters described above. Infusion of epinephrine is then stopped and with return of the blood pressure towards the preinjection level further records are made. The infusion of epinephrine may then be repeated. The velocity of blood flow in the strial vessels is measured by a method previously described. The microphonic response at 10 db steps between 80 and 110 db is recorded. Actual change in microphonic response, flow velocity in strial vessels and blood pressure are measured and compared. The experiment was terminated with intravital fixation of the temporal bones, subsequently sectioned and examined microscopically.

Observations on function. When the vena aqueductus cochleae is inter

rupted a few millimeters from the point where it leaves the basal turn, a small reduction (less than 10%) in flow velocity and microphonic response is noted. This is due to the collateral venous circulation including the vessels entering the internal meatus. These vessels join the inferior cochlear vein just at the bony wall of the basal turn and a lesion must be made at this point to include both the venous systems before a significant change in blood flow and microphonic response can be achieved. With a properly placed lesion a marked reduction in velocity of blood flow in all the exposed vessels is clearly evident. Even then, the effect is not uniform since the number and size of the veins draining the labyrinth (i.e. vena aqueductus vestibuli) are variable (see Nabeya).

The exposed terminal vascular units of the stria and spiral ligament are seen to change in several ways after occlusion of the inferior cochlear vein. Some passive dilation takes place in the flowing strial capillaries and veins due to increased venous pressure. There is a smaller change in the diameter of the radiating arterioles. Blood in a number of the strial capillaries may stop flowing in some cases without apparent damage to the vessel wall since flow may be resumed with the infusion of epinephrine. Flow in other vessels may be permanently interrupted. There was no leakage of blood cells from the exposed vessels. In many cases an overall slowing of blood flow results from this lesion. This reduced flow may continue with little change for the duration of the experiment except when briefly changed by epinephrine.

Accurate control over the amount and duration of blood pressure elevation is achieved by the use of a constant infusion pump for the intravenous administration of epinephrine. An increase in the velocity of strial blood flow may be regularly produced by elevation of the carotid blood pressure. The actual change in velocity in microns per second as well as the relative change following venous obstruction and infusion of epinephrine varies with the type of vessel. The behavior of flow in the radiating arteriole, a-v arcade and venule differs from that in the stria capillaries (see Tables 1 and 2). Thus an initial flow velocity of 253 μ per second in the radiating arteriole is reduced to 35 μ per second after venous obstruction. 1 minute after beginning infusion of epinephrine the velocity has risen to 48 μ per second, at 3 minutes it is 61 μ per second. On the other hand the flow velocity in the strial capillary with an initial value of 96 μ per second drops to 21 μ per second after venous obstruction. It rises to 29 μ per second 1 minute after infusion is started and to 43 μ per second 3 minutes after the start of infusion. Thus a 85% drop in flow velocity in the radiating arteriole after venous obstruction is compared with a 78% drop in the stria capillary. With epinephrine the velocity in the radiating arteriole can be increased 70% over the level following venous obstruction, while at the same time flow in the strial capillary shows an increase of 100%. It is reasonable to assume that similar changes in blood flow occur throughout the cochlea. The initial microphonic response to a 277 cycles stimulation at 90 db from differential electrodes across the cochlear duct in the basal turn of 1580 μ

TABLE 1 *Changes in microphonic response (basal turn). Strial blood flow, carotid blood pressure and heart rate after venous obstruction of the cochlea followed by infusion of epinephrine*

Time or condition	Before venous obst	Immediately after venous obstruction	During continuous infusion epinephrine 5 μg/kg/0.1 cc/min After 1 min	3 min	5 min	After stopping infusion 1 min	3 min
Cochlear microphonics in μV (peak to peak)	1580	700	820	1030	1090	810	690
Blood flow in μ/sec							
R.A. (7)	253	35	18	61	46	29	23
AVA (7)	233	13	73	98	75	19	40
Cap (7)	96	21	29	43	40	26	24
Ven (2)	210	22	58	68	41	36	17
Mean B.P. in mm Hg	60	55	87	86	46	46	41
Pulse pressure	28	28	33	35	28	25	22
Heart rate	290	280	290	290	290	250	270

R.A. = radiating arteriole. AVA = arteriovenous arcade. Cap = strial capillary. Ven = venule. Number following in parentheses indicates the number of separate vessels used in measurement of velocity.

TABLE 2

(Same as Table 1 except that microphonic responses were obtained by differential electrodes in the 3rd turn.)

Time or condition	Before venous obst	Immediately after venous obstruction	During continuous infusion epinephrine 5 μg/kg/0.1 cc/min After 1 min	3 min	5 min	After stopping infusion 1 min	3 min
Cochlear microphonics in μV (peak to peak)	680	270	350	440	450	370	220
Blood flow in μ/sec							
R.A. (8)	250	37	65	72	59	37	30
AVA (6)	240	39	89	75	73	36	33
Cap (3)	67	16	26	36	34	21	11
Ven (2)	210	19	25	25	22	20	17
Mean B.P. in mm Hg	55	57	90	87	70	40	40
Pulse pressure	25	22	33	35	29	25	23
Heart rate	270	270	285	290	295	275	265

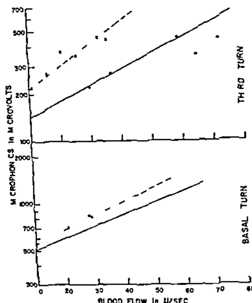


Fig 1 Relation between increase in cochlear blood flow and increase in cochlear function following obstruction of the vena aqueductus cochlea Blood flow rate was increased by the intravenous infusion of epinephrine × strial capillaries ● radiating arteriole For the 3rd turn the correlation coefficient between microphonics and blood flow in strial capillaries is 0 98 Stimulus 277 cycles at 90 db for 1st turn and 80 db for the third turn

volts drops to 700 μ volts or over 50 % immediately after venous obstruction and this is sustained With a rise in flow velocity induced by epinephrine the microphonic response improves An output of 1040 μ volts or 60 % of the normal value is recorded when the velocity of blood flow in the radiating arteriole has increased 70 % and in the strial capillary 100 % of the value immediately after occluding the inferior cochlear vein

If one plots the velocity of flow (arithmetic in the abscissa) versus the microphonic output (logarithmic) in the ordinate a curve relating flow to output is obtained which indicates a closer relation between changes in flow velocity in the strial capillaries than in the radiating arteriole and the microphonic output (see Fig 1) As infusion is continued at 3 min blood pressure usually begins to fall but is still 28 % above normal and at the same time there is a drop in flow velocity in the strial vessels Three min after infusion has stopped values for flow velocities and microphonic output return to the preinjection venous obstruction level

From differential electrodes in the third turn (see Tab 2) an initial 680 μ volts output in response to a 277 cycle stimulus at 80 db drops to 270 μ volts after venous obstruction At the same time a velocity of 250 μ per second in the radiating arteriole drops to 27 μ per second For the strial capillary the values are 67 μ per sec before and 16 μ per sec after venous obstruction and with infusion of epinephrine increases in these values are measured The

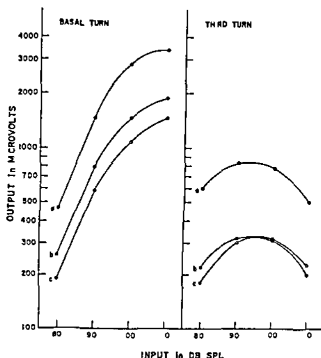


Fig 2 Stability and slopes of input output curves for a 277 cycle stimulus before (*a*) immediately after (*b*) and 2 hours after (*c*) occlusion of the vena aqueductus cochlea

microphonic response from the third turn retained the initial reduced value even after two hours of venous obstruction while in the basal turn the output after two hours was less than immediately after venous obstruction The initial drop in microphonic response immediately after venous obstruction in per cent was greater in the third turn than in the basal turn (see Fig 2) Blood pressure elevations of about 50 % were the maximum levels used in these experiments There was a close relation between blood pressure and flow velocity in cochlear vessels after obstructing the inferior cochlear vein The maximum effect on blood pressure was reached 1 min after onset of infusion While infusion was continued pressure dropped slowly When in*fusion was stopped pressure dropped rapidly to the preinjection level* There was a 2 min time lag between the peak of blood flow and the maximum microphonic response (see Figs 3 and 4)

HISTOLOGIC FINDINGS

The operated and unoperated ear together with the intervening brain stem were processed in one block so that significant abnormalities could be established by comparing cochlear details With the exception of the capillaries of the stria vascularis almost all of the cochlear vessels in these intravitally perfused specimens were empty (Fig 5 A C) The strial capillaries were *often* dilated and contained closely packed red cells (Fig 5*B D*) On the other hand the arterioles venules and A V arcades were empty The fluid spaces were usually clear although rupture of a strial vessel and

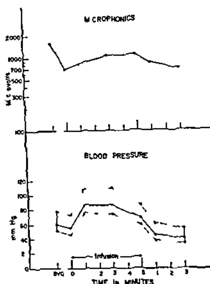


Fig 3 Relation between carotid blood and pulse pressure and microphonic response from the basal turns after venous occlusion BVO responses just before occlusion Blood pressure elevations produced by intravenous infusion of epinephrine

adjacent small collection of red blood cells were occasionally seen A more common finding was hemorrhage in the modiolus This was diffuse, surrounding the blood vessels including the posterior spiral vein, spiral ganglion and nerve trunk (Fig 5 *F*, *G*) but was not associated with hemorrhage in the subarachnoid space Compared with the unoperated side the stria, organ of Corti and spiral ganglion were normal (Fig 5 *B*, *F*)

DISCUSSION

The functional significance of the inferior cochlear vein (vena aqueductus cochleae) is again confirmed Severe changes in blood flow and function require that the vein be occluded at its exit from the cochlea where a tributary to the internal meatus is located It is also evident that all the venous drainage from the cochlea is not carried by these vessels because complete cessation of blood flow does not occur with this lesion Histological examination of these intravitally perfused specimens further emphasize the collateral venous channels from the cochlea All the blood vessels of the cochlea except the strial capillaries and some in the vestibular part of the labyrinth were empty of blood cells—indicating that despite the occlusion of the vena aqueductus cochleae the perfusion fluids introduced into the aorta moved into and through the terminal vascular bed, including the venous system Thus all the vessels of the modiolus were empty The posterior spiral vein was free of blood The vessels of the spiral ligament were also clear Only the strial capillaries appear to be occluded with red blood cells Some time

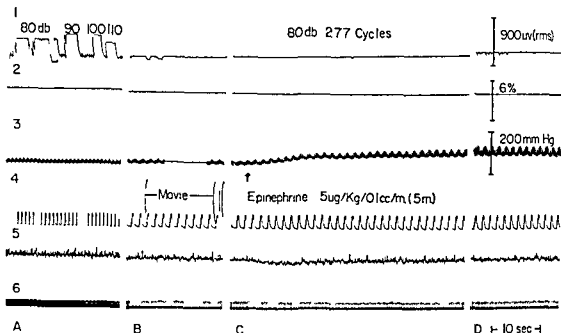
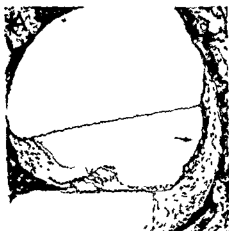


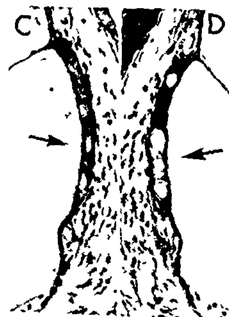
Fig. 4. Typical polygraph record. (1) Microphonic response from the third turn. (2) CO_2 in end expired air. (3) Blood pressure. (4) Respiratory pressure cycle. (5) E.E.G. (6) E.K.G. A, before; B, C and D, after obstruction of the vena aqueductus cochleae. D, after 3 min continuous infusion of epinephrine.

between the final recording of the reduced strial blood flow and the intravital perfusion through the open chest, complete stoppage of flow and sufficient capillary damage in the stria might result in a fixed thrombus that could not be dislodged from the strial capillary with the perfusion fluid introduced at about 70 mm Hg pressure. Otherwise the temporal bone sections were not remarkable except for hemorrhage in the modiolus and an occasional small vessel rupture with a minute hemorrhage in the adjacent cochlear duct. The strial capillaries were often dilated. Hemorrhage in the modiolus resembled that seen in earlier venous obstruction experiments. Unlike some of the earlier findings in the present series there were no large hemorrhages in the fluid spaces of the labyrinth. Hemorrhage in the modiolus was probably due to rupture of some of these vessels. Blood cells were found surrounding the empty posterior spiral vein in its bony canal. Since there was no blood in the subarachnoid space, the blood in the modiolus did not come from the subarachnoid bleeding. Additional collaterals such as the vein along the endolymphatic duct are probably responsible for sustaining some degree of flow after occlusion of the vena aqueductus cochleae, although this is in

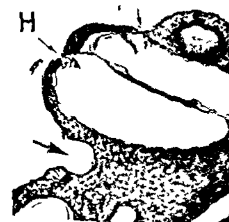
Fig. 5. A, Normal cochlear duct. B, After disruption of the vena aqueductus cochleae. C, D, high magnification of [illegible]. Arrows indicate stria vascularis. E, Normal [illegible]. F, Hemorrhage in the modiolus after venous obstruction. G, red blood cells surround the posterior spiral vein. H, Electrode holes in scala vestibuli and scala tympani of basal turn (small arrows) and surgical defect in the bone (large arrow) to destroy the vena aqueductus cochleae. I, Electrode holes (arrows) in scala vestibuli and scala tympani of third turn.

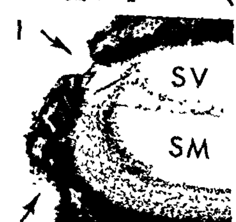





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adequate for normal flow or normal function (microphonic response). Unlike the rapid deterioration of function with complete cessation of flow as found with arterial obstruction (Perlman *et al.* 1959), a significant (50% of normal) microphonic output can be sustained even when velocity of blood flow in the strial vessels has dropped markedly. There is a difference between the arteriole and capillary in this regard. While flow in the arteriole is reduced to 15% of normal, in the strial capillary it may be 20% of the normal value. *The smaller effect in the strial capillary may be due to cessation* of flow in some capillaries and venules thus reducing the number of outflow channels. There is no reflex arteriolar contraction associated with *this degree of venous obstruction.* Denny Brown (1956) reports that retrograde pressure from the cerebral capillaries in counter perfusion experiments through a cerebral vein can cause severe arteriolar spasm. Sudden venous occlusion in the limb produced a similar result and this spasm in the limb vessels could be blocked by paralysis of the sympathetic (Pereira 1946). Slowing of arterial and arteriolar blood flow due to venous obstruction in the bat wing is reported by Wiedmann (1959). She thinks it is a mechanical effect rather than the result of vasoconstriction because it did not change *with denervation. She reports that distension of the vein increases its vaso*motion. We did not see evidence of vasomotion in the venules in the spiral ligament exposed by the fenestra. Yamada & Burton (1954) state that local obstruction of a peripheral vein produces constriction of *the arterioles* supplying the particular venous bed.

Reduction in strial blood flow following venous obstruction results in a decrease in rate of oxygen delivery to the cells. Reduction in cerebral flow by occlusion of the jugular veins causes a rise in CO_2 and drop in O_2 and a decrease in pH according to Meyer (1962). He found that the changes due to reduced blood flow in experimental embolism lead to abnormal cation (sodium and potassium) shifts that are important in the bioelectric potentials generated by cortical cells. With improved blood flow there was return towards normal in cations within the cell. Similar cation shifts in cochlear hair cells may explain the changes in microphonic output following changes in flow velocity and resultant anoxia and acidosis. The relationship between cochlear microphonic output, blood pressure and cochlear blood flow after venous obstruction are complicated but indicates the importance of flow *in the strial capillary. There is a time lag between the peak of blood flow* and the peak of microphonic output. In the thyroid gland, Söderberg (1958) found a time lag between blood flow, iodine uptake and hormone release.

Sustained reduced microphonic output with a constant reduced level of blood flow suggests a sustained reduced metabolism of the hair cell and the cells of the stria vascularis. What aspects of cell metabolism and what cells of the cochlear duct are involved to effect the reduced response is not known. Histologic changes seen with chronic venous obstruction include degeneration of the outer hair cells and the cells of the stria vascularis. Sustained reduced metabolism may be temporarily increased with temporary

increase in blood flow. Fales (1962) reports that there is reduced oxygen consumption in muscle with partial venous occlusion and that with release of obstruction there is no repayment of the oxygen debt and no supernormal phase of blood flow. In release of arterial occlusion there is repayment of the oxygen debt and blood rushes into a dilated bed with reduced resistance. We have reported this reaction on release of obstruction of the internal auditory artery.

It is evident that blood flow was reduced by venous occlusion below the level that could sustain normal cochlear function *even if all the oxygen* could be extracted from the blood as it flowed through the strial capillaries. According to Elliot (1946) the rate of oxygen consumption in living cells is independent of oxygen tension down to very low levels (i.e. less than 4 mm Hg) for rat brain suspension. The brain cells require very small amounts of oxygen (i.e. 1 mm O_2 tension) to carry out electron transfer by the respiratory chain of enzymes according to Chance (1962). With a drop in intracellular oxygen tension to 0.2 *mm Hg* a 50 % reduction in brain cell respiration measured as reduction of pyridine nucleotide in mitochondria is reported by Chance. The concentration of oxygen in *inspired air* of 4 % partial pressure (30 mm Hg) sustained this reduced metabolism of the brain cell. Chance reports that the first change in brain cell respiration occurs when the animal is exposed to 8 % O_2.

ZUSAMMENFASSUNG

Die funktionelle Bedeutung *der intracochlearen* Vene *wird erneut* festgestellt. Nach der Okklusion *der intrachochlearen* Vene lasst *sich eine bedeutende* Abnahme der Mikrophonopotentiale und des *cochlearen* Blutstroms feststellen. Die nach der venösen Okklusion durch Epinephrin hervorgerufene Zunahme des cochlearen Blutstroms ist von einer *Zunahme* der Mikrophonpotentiale begleitet. Zusammenhänge zwischen Blutstrom, Sauerstoffausnutzung und Zellfunktion *werden* besprochen.

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DIURNAL VARIABILITY OF AUDITORY THRESHOLD

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The absolute threshold for hearing was measured at 7 a.m., noon, 5 p.m., and midnight for 4 days on 6 listeners. No diurnal periodicity appeared, indicating that time of day *per se* does not constitute a significant source of variance in studies using absolute sensitivity as the dependent variable.

Recent research has indicated that many physiological functions show cyclic changes with a period of about 24 hours (Anonymous, 1961). For example, Halberg and his collaborators (1960) have shown that the incidence and severity of audiogenic seizures in certain strains of mice are dependent on some underlying diurnal cycle, being greater when the seizure arousing stimulation is presented early in the "dark" portion of the light-dark cycle. This suggests the possibility that other aspects of auditory function may also display a diurnal rhythm, and leads to the specific experimental question of concern here: *Does auditory sensitivity* (i.e., the absolute threshold) *of human listeners vary with time of day?*

Until last year, the scant published evidence seemed to indicate a negative answer. Although there is always a certain amount of variability associated with repeated testing of auditory threshold, no one had been able to show that any of the variance could be attributed to temporal factors. For example, neither Wertheimer (1953) testing once a day over a period of weeks, nor Harris & Myers (1954) measuring hourly from 8 a.m. to 4 p.m., found any detectable periodicity. However, in 1962 Neuberger & Schmid (1962) claimed to have found a diurnal variability of 10 to 15 decibels (dB), threshold for air conducted tones being lowest (most sensitive) at noon and highest at midnight, with a reversed situation for bone conducted tones (most sensitive at midnight). Although in their articles no description was given of the test apparatus, procedure, or subjects, caution properly demanded that the question of diurnal periodicity be reopened, since no other investigators had employed systematic testing at midnight.

PROCEDURE

Accordingly, thresholds at 500, 1000, 2000, 3000, 4000, and 6000 cycles per second (cps) were measured on the left ears of 6 listeners (5 medical students and the author) at approximately 7 a.m., noon, 5 p.m., and mid

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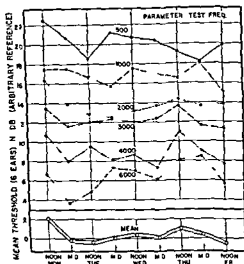


Fig. 1

bility of threshold sensitivity due to endogenous factors may *never* exist. If one ran a careful series of tests at frequent intervals on a great number of individuals over a long period of time, one might find a few persons with a large diurnal cycle; perhaps the subjects of Neuberger and Schmid fit this category (if no peculiarity of procedure can be found to account for their results). Possibly, even the average group results might reach statistical significance. However, the best prediction one can make from the present results is that diurnal variability will never be an *important* determinant of auditory sensitivity. We may therefore continue to perform experiments in which the absolute threshold is the dependent variable, such as studies of auditory fatigue following exposure to intense sound, with no concern over

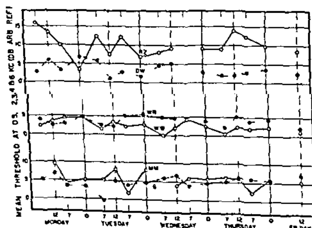


Fig. 2

night (except for unavoidable omissions), beginning at noon Monday and proceeding until noon Friday. None of these listeners were exposed, during the day, to loud sounds that might produce appreciable auditory fatigue. It can be seen that if such loud sounds were experienced every day (for example, if the listener drove a motorcycle several miles before the midnight test), one might well detect a diurnal periodicity of threshold, but this periodicity would be due to auditory fatigue rather than some underlying cyclic physiological variable.

The modified method of limits was used to determine threshold: the listener controlled, by means of a pushbutton, the direction of movement of a variable recording attenuator whose attenuation was always either increasing or decreasing (at a rate of 1 dB/sec, in this case). "Threshold" was defined as the point halfway between the median ascending and median descending reversal points. The auditory stimulus consisted of a continuous train of 250-msec pulses separated by 250-msec silent intervals, presented through one of a pair of Permoflux PDR-8 earphones in MX-41/AR cushions. The listener was seated inside a commercial double-walled sound booth, while the experimenter and all apparatus were outside. No detectable outside noise reached the listener at any time of the day. Signal level was carefully calibrated, and monitored at all times.

RESULTS AND DISCUSSION

The average results for the group are presented in Fig. 1. The top portion of Fig. 1 shows the course of the mean thresholds at each of the 6 test frequencies at noon and midnight throughout the week; the grand mean of all 6 frequencies is shown at the bottom of Fig. 1. The arbitrary reference point for each curve was chosen simply to keep all curves separated. Clearly, there is no evidence of the diurnal variability of 10 to 15 dB reported by Neuberger and Schmid.

However, it is possible that each listener might have his own unique individual cycle of sensitivity, so that each person might have a different time of maximum or minimum sensitivity. If this were the case, then an average curve such as that shown in Fig. 1 would be inappropriate. Therefore the individual data are presented in Fig. 2. Here the average threshold over the 6 test frequencies (again relative to an arbitrary reference point) for each observer is shown as a function of time. Diurnal cycles are certainly not readily apparent. Values of the standard deviation, over the entire testing period, of repeated tests at a single frequency on a single ear, were about the same as those typically observed with similar apparatus when the testing is done once a day or once a week, but at the same time of day (i.e., about 2 dB at test frequencies through 3000 cps, 3 dB at 4000 and 6000 cps). Thus no appreciable variance was added by testing at four different times of day.

The present results do not, of course, prove that inherent diurnal varia-

PERCEPTION OF THE POSTURAL VERTICAL FOLLOWING PROLONGED BODILY TILT IN NORMALS AND SUBJECTS WITH LABYRINTHINE DEFECTS[1,2]

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Nine normal men and ten men with defective labyrinthine function were studied in order to determine the effects of prolonged bodily tilt on their perception of the postural vertical The subjects were tested under two conditions of delay before setting themselves to vertical and four degrees of tilt A 2 × 2 × 4 analysis of variance showed significantly greater average errors for the labyrinthine defective men for prolonged delay in recovery to vertical and for the larger tilts

Subjects with normal vestibular function can set themselves to the postural vertical with extraordinary accuracy in the absence of visual cues when seated in a tilting chair (Clark & Graybiel 1963 Clegg & Dunfield 1954 Garten 1920 Pearson & Hauty 1960 Solley 1960) Even subjects with defective vestibular function can perform this task fairly well (Clark & Graybiel 1963 Garten 1920) A variety of experimental variables have been shown to contribute to the accuracy of this task and although there is not complete agreement among investigators the following are some which have been reported as important repeated trials (Clark & Graybiel 1963 Pearson & Hauty 1959 Solley 1956) rate of rotation in setting to the vertical (Clegg & Dunfield 1954) magnitude of tilt (Clegg & Dunfield 1954 Mann & Passey 1951 Pearson & Hauty 1960) and duration of the delay at a given tilt before returning to the vertical (Mann & Passey 1951 Passey & Guedry 1949)

It has been generally assumed that the vestibular mechanism plays an important role when the subject sets himself to the postural vertical but the evidence indicates that differences in errors between normals and subjects with defective vestibular function are small (Clark & Graybiel 1963 Garten 1920) Similar results have been reported for other tasks which require the perception of the vertical (Brown 1961 Padden 1959) Relatively little

[1] Opinions or conclusions contained in this report a[illegible]
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[2] [illegible] Grant R 37

the fact that the pre exposure threshold may have been measured in the morning, the post exposure threshold in the afternoon, for example Whether this lack of dependence of peripheral sensitivity on the time of day *per se* holds only for hearing, or is characteristic of sensory thresholds in general remains to be seen

ZUSAMMENFASSUNG

Die Hörschwellen von 6 Personen wurden um 0700, 1200, 1700, und 2400 Uhr während 4 Tagen gemessen Es gab kein Vorkommen von Periodizität in der Empfindlichkeit Also ist die Tageszeit ohne Beziehung zu den Forschungen, welche die absolute Hörschwelle benutzen, z B die Messungen von Hörermüdung

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[2] This research was conducted under the sponsorship of the Office of Life Science Programs U S National Aeronautics and Space Administration Grant R 3[illegible]

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1963). Since the otolith function of the deaf subjects was not clearly defined, they will simply be designated as labyrinthine defective.

Procedure

Subject's task was to return himself to the postural upright on signal from the experimenter following various degrees of tilt to the right or left. All of the subjects were familiar with the task since they had participated in a study which required them to make 30 similar settings to the postural vertical in the absence of a visual framework (Clark & Graybiel 1963). The subject was told that his task was the same as in the preceding tests and that he would be permitted no more than twenty seconds to make the adjustment. If a longer time was taken, the trial was repeated, but this happened rarely. Typically, the subject brought himself rapidly most of the way to the vertical, paused, and then made the final adjustment slowly, completing the setting well within the twenty second limit. Each series of trials was given as follows. Subject sat in an upright position in the chair and when he signaled he was ready, the chair was tilted to the right. As soon as the chair reached the appropriate tilt, experimenter signaled subject who immediately set himself to the upright, and the error was recorded. Experimenter then tilted subject the same amount to the left. Ten settings to the upright were made from 10°, 20°, 30° and 40°, alternating right and left tilts, 40 settings being made in one session. This series of settings was termed the *zero delay series*. After a rest period a corresponding series of settings was made in the same order except that the subject was held in the tilted position for two minutes before he returned himself to the vertical. This series was called the two minute delay series. Settings for 10° and 20° were made in one session, and after a rest period corresponding settings were made at 30° and 40°. Following suitable rest periods three more series of settings were made in three separate sessions except that the order of tilt was changed to 40°, 30°, 20 and 10, for both the zero delay and two minute delay settings. Rest periods with subjects seated erect were given half way through each session. This procedure resulted in ten trials for each delay period, each direction of tilt, and the four positions of tilt.

RESULTS

The first analysis of the data was made by comparing the average errors in settings from tilts to the right and to the left. None of these differences was found to be significant, confirming earlier studies by Passey and Guedry (1949), Pearson and Hauty (1959) and Solley (1960). The following analysis is therefore based upon the combined data from right and left tilts for two groups of subjects, two delay periods, and four degrees of tilt.

The mean average errors (in degrees) in settings for the three experimental conditions are summarized in Table 1. To test the significance of these differences, a three factor (2 × 2 × 4) analysis of variance for repeated measures was performed (Winer 1962). All of the primary variables showed signifi

specific data are available, however, concerning the specific function of the vestibular receptors in setting to the postural vertical The reason for this is not hard to find Anatomically, the vestibular mechanism and the otoliths in particular are not only remote, but they are also functionally interrelated with other sensory processes, and it is not possible to stimulate them without stimulating other receptors Subjects with defective labyrinths are difficult to obtain Deaf subjects have been used, but a substantial percent of them have some vestibular function (Arnvig, 1960, Garten, 1920) It was, therefore, the purpose of this study to compare the effect of prolonged bodily tilt of varying amounts on the perception of the postural vertical in normals and in subjects with defective vestibular mechanisms to obtain additional data concerning the function of the otoliths in the perception of the postural vertical

METHOD

Apparatus

The apparatus has been described in detail elsewhere (Clark & Graybiel, 1963) It consisted of a large, tilting chair with padded seat which was controlled by either experimenter or subject turning a knob The pressure on the knob controlled the speed of a hydraulic motor which tilted the chair, the typical recovery velocity being of the order of 2–3 RPM It should be noted that this velocity was substantially greater than the velocities used in other studies (Clegg & Dunfield, 1954) The subject was strapped firmly in position in the seat by means of a seat belt, shoulder straps, and a rigid head rest The position of the chair could be read by the experimenter from a dial to an accuracy of one-half degree The experimental room was darkened for all tests, and the subject s eyes were covered with eye patches

Subjects

Nine normal young men and ten deaf men with vestibular defects from Gallaudet College were studied Medical examination revealed that they were all in good health All of the normals had normal hearing exhibited normal responses to passive rotation, and perceived the oculogravic illusion All of the deaf subjects had acquired their deafness in childhood as a sequela of meningitis Seven of them had residual hearing when exposed to high intensity noise Although none of them exhibited definite nystagmus as a result of caloric stimulation (ice water) questionable nystagmic beats (not sustained) were recorded in three Tests of otolith function using the oculogravic illusion (Graybiel, 1952) revealed significant individual differences, some overlapping the values obtained from normal subjects (Graybiel & Clark, 1962) The results of otolith function using ocular counterrolling showed no overlap with the values obtained from normal subjects (Miller & Graybiel, 1963) A series of practice trials during which the subjects made 30 settings to the postural vertical showed clear learning effects and very little difference between the two groups after 15 settings (Clark & Graybiel,

earlier studies (Clegg & Dunfield, 1954; Pearson & Hauty, 1960). It is suggested that these results are primarily dependent upon two unique conditions of this experiment, firstly, the rather long time subjects were held in the tilted position and secondly, the rapid rate of recovery to the vertical position. Most earlier studies maintained the subjects in the tilted position well under the two minute period used in this study. It is suggested, however, that the primary factor was the rapid rate of recovery used in this experiment. Earlier studies used recovery rates of the order of 4°–28° per minute whereas the present study involved rates of the order of 2–3 RPM. Such slow recovery rates (e.g. Clegg and Dunfield, 1954) would permit ample time for readjustment processes in the sensory mechanisms involved while the rapid recovery rates would be expected to reduce such effects. It should be re-emphasized that the twenty second adjustment time was more than adequate to permit subjects to be satisfied with their settings and that trials had to be repeated only three or four times throughout the whole study. Furthermore, with a rapid recovery rate the amount of time required to bring the chair to the vertical was very close to the same for all tilts. These results suggest that the two minute tilt results in adaptation effects in the tactual and/or proprioceptive receptors. There is evidence that the oculogravic illusion, which is believed to be an indicator of otolith function (Graybiel, 1956), exhibits no adaptation effects even over a four hour period of constant stimulation on a centrifuge (Clark & Graybiel, 1962). Hence for the normal subjects, information from the otoliths is adequate to compensate partially for the adaptation effects while the labyrinthine defective subjects do not have this information available and therefore the adaptation effects result in maximal errors.

Although this experiment was not immediately concerned with the directional effects in setting to the postural vertical, data were available on this point. When the direction of the setting was taken into account, the mean setting for each group and each of the four tilts was always in the direction the chair was tilted for the two minute delay. The data for the zero delay in returning to the postural vertical were in the same direction, but there was one exception out of the eight mean scores for each group which showed a reversal of this directional effect. These results tend to support the findings of Fleishman (1953) whose subjects showed a clear tendency to set the chair in the direction of the tilt.

ZUSAMMENFASSUNG

Neun normale Männer und zehn Männer mit defekter Labyrinthfunktion wurden untersucht, um die Auswirkungen länger andauernder Körperneigung auf ihre Perzeption der posturalen *Vertikale festzustellen*. Die Versuchspersonen wurden unter zwei Verzögerungskonditionen getestet, bevor sie sich selbst zur Vertikale und in vier verschiedene Neigungsgrade setzten. *Eine* 2 × 2 × 4 Analyse der Veränderung zeigte erheblich grössere Durchschnittsfehler für die labyrinthdefekten [illegible] länger andauernde Verzögerung in Wiederherstellung der Vertik[illegible] Neigungen.

…ul mechanical

TABLE 1 *Average errors in degrees in setting to the postural vertical*

Delay in setting	Normal subjects (N = 9) Tilt 10°	20°	30°	40°	Labyrinthine defective subjects (N = 10) Tilt 10°	20°	30	40
0	1.2	1.5	2.0	1.9	2.4	2.7	3.0	3.3
Two minutes	2.2	3.5	3.8	4.2	3.4	6.1	6.5	6.8

cant *F*s as follows normal versus vestibular defective ($F = 11.56$ d.f. 1/17 $p < 0.01$) zero versus two minute delay ($F = 209.09$ d.f. 1/119 $p < 0.01$) and degree of tilt ($F = 22.47$ d.f. = 3/119 $p < 0.01$). Only two of the interactions showed significance above the 0.05 level as follows subjects × delay interaction ($F = 9.94$ d.f. = 3/119 $p < 0.01$) and delay × tilt interaction ($F = 7.13$ d.f. = 3/119 $p < 0.01$). These interactions show that the labyrinthine defective subjects made significantly greater errors following the two minute delay and that the effects of the two minute delay were significantly greater for the greater tilts. The subjects × tilt and the subjects × delay × degree of tilt interactions were not significant.

These results offer convincing evidence that under the conditions of this experiment labyrinthine defective subjects make significantly greater errors than normals. Furthermore they demonstrate that the error in setting is a function of both the degree of tilt and the duration of the delay before the subject returns himself to a vertical position. It is worth noting that the mean average error for the settings at 30° of tilt and zero delay for both groups (Table 1) is only slightly greater than the results for these subjects after 30 successive trials reported in an earlier study (Clark & Graybiel 1963).

DISCUSSION

Although these results give further evidence that normal subjects make smaller errors in setting to the postural vertical than do subjects with defective labyrinthine function for the most part these errors are small even for the latter group. Indeed the largest single error made by the labyrinthine defective group was 17° while that for the normal group was 14°. These errors were considerably less than those reported by Brown (1961) even for normal subjects during water immersion to simulate zero gravity. The more accurate performance in the present experiment is no doubt related to tactual and proprioceptive cues available to the subjects. The tactual cues including those from the straps and rigid head rest could be expected to facilitate the task (Fleishman 1953). The finding that both groups produced greater error with increasing tilt was to be expected and is supported by earlier studies of normals (Fleishman 1953 Pearson & Hauty 1960).

The results showing a greater error in setting to the postural vertical following prolonged bodily tilt are not in accord with the findings of some

earlier studies (Clegg & Dunfield, 1954 Pearson & Hauty, 1960) It is suggested that these results are primarily dependent upon two unique conditions of this experiment, firstly, the rather long time subjects were held in the tilted position and secondly the rapid rate of recovery to the vertical position Most earlier studies maintained the subjects in the tilted position well under the two minute period used in this study It is suggested, however, that the primary factor was the rapid rate of recovery used in this experiment Earlier studies used recovery rates of the order of 4°–28° per minute whereas the present study involved rates of the order of 2–3 RPM Such slow recovery rates (e g Clegg and Dunfield, 1954) would permit ample time for readjustment processes in the sensory mechanisms involved while the rapid recovery rates would be expected to reduce such effects It should be re emphasized that the twenty second adjustment time was more than adequate to permit subjects to be satisfied with their settings and that trials had to be repeated only three or four times throughout the whole study Furthermore, with a rapid recovery rate the amount of time required to bring the chair to the vertical was very close to the same for all tilts These results suggest that the two minute tilt results in adaptation effects in the tactual and/or proprioceptive receptors There is evidence that the oculogravic illusion which is believed to be an indicator of otolith function (Graybiel 1956) exhibits no adaptation effects even over a four hour period of constant stimulation on a centrifuge (Clark & Graybiel 1962) Hence for the normal subjects information from the otoliths is adequate to compensate partially for the adaptation effects while the labyrinthine defective subjects do not have this information available and therefore the adaptation effects result in maximal errors

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THE AETIOLOGY OF ACUTE MIDDLE EAR INFECTION

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Five hundred and sixty three specimens taken by the puncture aspiration technique from patients suffering from acute middle ear infections during two periods 1956–1957 and 1962–1963 were cultured for the detection of micro organisms. Virological techniques were employed also in the first period. The investigations reveal that *Diplococcus pneumoniae*, *H. influenzae* and *Strept. pyogenes* are still the most common causative organisms in acute middle ear infection and that *Staph. aureus* is of lesser importance than has been claimed. Acute middle ear infection is almost always a monomicrobic infection. PPL organisms and virus were not found with the techniques employed.

As it seems to have become widely accepted in recent years that *Staphylococcus aureus* is a common, if not the most common, organism causing middle ear infection (McNeill 1962, Mawson 1963), the authors consider it justified to present the results of studies on the aetiology of acute middle ear infection in a series in which particular attention was paid to the technique of taking specimens.

MATERIAL

The patients examined were those who came because of ear symptoms to the clinic of the Department of Otolaryngology, University of Turku, the Ear Clinic of the Turku Public Schools or to the reception of a physician participating in the study during periods from May 1956 to June 1957 and from January 1962 to September 1963. No conscious selection of the patients was made. The age distribution of the patients is shown in Table 1. Of the 460 patients examined 247 had a unilateral and 213 a bilateral otitis (Table 2). The number of specimens examined was 563. Table 2 reveals further that specimens from both ears were taken from 103 patients and from only one ear from 110 patients. The reason why a specimen was obtained from only one ear was that the specimen could not be taken with the chosen technique, for example, because spontaneous rupture of the tympanic membrane had occurred before the patient arrived for treatment.

METHODS

The specimens from the middle ear were taken by the puncture aspiration technique described by Lahikainen (1953) after a careful mechanical clean

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The following examinations and tests were carried out to identify the isolated micro-organisms. Haemophilae were diagnosed when the morphology and colony characteristics were typical and the isolated strains were differentiated on the basis of their ability to grow on media containing X and V growth factors (Mackie & McCartney, 1953). Encapsulated strains were detected by means of the iridescence phenomenon on Levinthal agar according to Engbæk (1950) and typed with immune sera against types a–f.

Micrococci were diagnosed on the basis of typical morphology and colony characteristics and hemolysing power, pigmentation, ability to produce α toxin, coagulase, phosphatase and gelatinase and ability to ferment mannitol (Mackie & McCartney, 1953). Pneumococci were identified by means of a positive bile test and typed with diagnostic sera from the Statens Serum Institut, Copenhagen. The classification of Swift (1952) was employed when differentiating aerobic streptococci.

Neisseriae identified from typical morphology, colony characteristics and results of the oxidase test were differentiated by testing their ability to ferment glucose, maltose, lactose and saccharose (Mackie & McCartney, 1953). Gram-negative rods of the Family *Enterobacteriaceae* were identified by the aid of the biochemical reactions and classification system of Kauffmann (1954).

Virus isolation

For the isolation of viruses specimens of middle ear exudates collected in 1956–1957 were inoculated into HeLa cell cultures, stationary tubes and embryonated eggs after fourfold dilution with Parker's medium containing penicillin and streptomycin. Before the inoculation the four-day-old HeLa cell cultures had been washed twice with Hanks' solution. A 0.8 ml volume of culture medium consisting of 10 per cent horse serum in Parker's medium was added to each of 2–4 tubes followed by 0.2 ml of the diluted specimen. One hundred specimens found negative on staining and culture and 226 specimens that yielded bacterial outgrowth were tested in HeLa cell cultures. As far as possible, the specimens were inoculated immediately on their arrival at the laboratory. When cultures were not ready for inoculation, the specimens were stored at −20°C. The maximum storage time was 15 months. Forty-eight of the above mentioned 100 specimens found negative on staining and culture were cultured in serial passages. The microscopical examination of the tubes was performed at intervals of two to four days and considered negative if no cytopathogenic effect was noted by the eighth day. Several adeno virus strains were propagated simultaneously as controls.

Furthermore diluted specimen was inoculated into two embryonated eggs. Up to September 1956, 0.2 ml of the diluted specimen was injected into the allantoic cavities of two 7–10 day old eggs and subsequently into amniotic cavities of two 10–11 day old embryos. The inoculation of the amniotic cavity was carried out by the method described elsewhere (Mackie & McCartney, 1953). Fifty-eight specimens of which 28 were negative on stai

TABLE 1 *Acute middle ear infections in different age groups in the series of 1956–1957 (I) and 1962–1963 (II)*

Age group	No. of patients I	%	II	%	Total
<1	38	11.8	12	8.7	50
1–6	123	38.2	55	39.9	178
7–14	133	41.3	38	27.5	171
≥15	28	8.7	33	23.9	61
Total	322	100.0	138	100.0	460

TABLE 2 *Number of cases of unilateral and bilateral acute middle ear infections in the series of 1956–1957 (I) and 1962–1963 (II)*

	No. of patients			No. of specimens		
	I	II	Total	I	II	Total
Unilateral	176	71	247	176	71	247
Bilateral	146	67	213	223	93	316
Total	322	138	460	399	164	563

ing of the external meatus. Drainage of middle ear was completed by suction through the punctured whole. General divinyl ether anaesthesia was used for infants, whereas local anaesthesia with Bonain's solution was employed in the case of the older patients. The syringes with the withdrawn middle ear exudates were immediately taken to the Department of Microbiology, where the specimens were cultured within not more than three hours, within one hour in most cases. The plunger of the syringe was removed and the exudate was transferred with a platinum loop to several culture media for the isolation of different microorganisms. When the amount of exudate was not large enough for it to enter the syringe, the exudate was forced with air from the needle onto blood agar and specimens were transferred from the resulting globule to the other culture media.

A slide prepared from the exudate was stained by the Gram procedure. The culture media were blood agar, McLeod chocolate agar, liver broth and, for the detection of PPLO organisms, Difco PPLO agar and PPLO broth. The McLeod chocolate agar cultures were incubated in a CO_2 atmosphere at 37°C, the others in air at the same temperature. The cultures were examined daily during an incubation period of 1–3 days. The liver broth cultures were considered negative if no growth was noted during one week. A PPLO agar culture was taken to be negative if no growth occurred during one week. The PPLO broth cultures were incubated for ten days and considered negative when after inoculation of PPLO agar no growth occurred.

TABLE 3 *Distribution of monomicrobic and polymicrobic infections in the series of 1956 1957 (I) and 1962 1963 (II)*

Infection	No of specimens I	%	II	%	Total	%
Monomicrobic	233	59.9	101	61.7	340	60.4
Polymicrobic	18	4.6	11	6.7	29	5.1
Staining positive culture negative	30	7.5	3	1.8	33	5.9
Staining and culture negative	112	28.1	49	29.8	161	28.6
Total	399	100.0	164	100.0	563	100.0

TABLE 4 *Monomicrobic specimens from acute middle ear infections in the series of 1956 1957 (I) and 1962 1963 (II)*

Causative organism	No of specimens I	%	II	%	Total	%
Haemophilus influenzae	42	11.0	41	26.8	83	15.6
Haemophilus parainfluenzae	1	0.3			1	0.2
Staphylococcus aureus	10	2.6	1	0.6	11	2.1
Staphylococcus albus			3	1.9	3	0.5
Neisseria catarrhalis	5	1.3	2	1.3	7	1.3
Diplococcus pneumoniae	121	31.8	36	23.4	157	29.4
Streptococcus pyogenes	55	14.4	13	8.5	68	12.7
Streptococcus viridans	4	1.0	5	3.6	9	1.7
Pseudomonas	1	0.3			1	0.2
Staining positive culture negative	30	7.9	3	1.8	33	6.2
Staining and culture negative	112	29.4	49	32.0	161	30.1
Total	381	100.0	153	100.0	534	100.0

general rule the acute otitis media in both ears usually has a common aetiology

With the exception of six strains the isolated H influenzae strains were non encapsulated The six strains were all of type b two of these were isolated from patients with unilateral and three from patients with bilateral otitis Both exudates of *one patient* contained *H influenzae* type b together with *Diplococcus pneumoniae* of type I and the exudates of a second patient with unilateral otitis and of a third patient with bilateral otitis contained the *H influenzae* type *b* and *Diplococcus pneumoniae* type XIX The remaining two encapsulated strains were the only species in their respective specimens

ning and culture were tested in the former manner and 57 specimens of which 44 were negative on staining and culture in the latter manner. The inoculated eggs were incubated for three days at 37°C. Specimens from the embryos inoculated with the 44 bacterially negative specimens were taken on the third day from the allantoic or amniotic cavities and inoculated repeatedly into fresh amniotic cavities.

Samples of the allantoic fluids and amniotic fluids (the latter from September 1956) were diluted 1:20 to 1:640, and tested for haemagglutination using chicken erythrocytes. The haemagglutination tubes were kept at room temperature for one hour and then read. Influenza strain A Finlandiae a NCD strain, and a mumps virus strain P 44 were employed as controls.

RESULTS

The majority (60.4 per cent) of the examined middle ear exudates were found to contain only one bacterial species (Table 3). Two or more bacteria were isolated from only a few of the exudate specimens (5.1 per cent) and hence the proportions of specimens which were negative on staining and culture was high (28.6 per cent). The last mentioned specimens are called "non-bacterial" in the following.

The incidence of different bacterial species in the exudates from which only one species was isolated is shown in Table 4. The bacteria most often isolated from the exudates were *Diplococcus pneumoniae* (29.4 per cent), *Haemophilus influenzae* (15.5 per cent) and *Streptococcus pyogenes* (12.7 per cent). One of these three species was isolated from 80.5 per cent of the 382 specimens that were positive for bacteria. Other bacterial species were present in only a relatively few specimens. Noteworthy is the low incidence of *Staphylococcus aureus* and that this incidence was no higher in the second than in the first time period.

The results for those specimens which were found to contain more than one bacterial species are listed in Table 5. Also in this group of specimens the incidence of *Staphylococcus aureus* was at most half as high as that of pneumococci or *Haemophilus influenzae*.

The specimens from 77 patients with bilateral acute otitis media from whom specimens were obtained from both ears were examined more closely. The bacteriological finding was identical for both ears in 51 patients. In the case of 9 patients the specimen from one ear was found to contain bacteria and the specimen from the other ear gave a positive reaction on staining but no bacteria grew on culture. A bacterium was isolated from one of the specimens from the two ears of 11 patients but the other specimen was negative on both staining and culture. The middle ear exudates of both ears of one patient contained *H. influenzae* and one of the two exudates also *Staphylococcus aureus*. The bacteriological findings for the two specimens were quite different for only one patient: *Streptococcus pyogenes* was identified in one and *Staph. aureus* in the other exudate. It may hence be taken as a

TABLE 7 *Distribution of bacteria from monomicrobic infections in different series during the period 1948 1963*

Causative organism	Lahikainen 1948 51	%	Heikkila & Peltonen 1954	%	Present series 1956-57	%	Present series 1962-63	%
H influenzae et parainfluenzae	112	*18 4*	29	*24 3*	43	*18 0*	41	*40 6*
Staphylococcus aureus	13	*2 7*	14	*11 9*	10	*4 2*	1	*1 0*
Diplococcus pneumoniae	282	*46 3*	50	*42 5*	121	*50 6*	36	*35 6*
Streptococcus pyogenes	177	*29 1*	17	*14 4*	55	*23 0*	13	*12 8*
Varia	24	*3 5*	8	*6 9*	10	*4 2*	10	*10 0*
Total	608	*100 0*	118	*100 0*	239	*100 0*	101	*100 0*

was found between the duration of disease before the drum puncture and the incidence of non bacterial otitis

We did not succeed in isolating PPL organisms or viruses from the middle ear exudates by the methods employed

DISCUSSION

The results of previous studies carried out in the same departments and our results for different time periods are shown in Table 7 Only results for specimens from monomicrobic infections were included in the comparison as these specimens were taken to reveal the true aetiologic factors of acute bacterial middle ear infection In spite of the fact that the age distribution of the series differ and hence influence the results the pneumococci show a

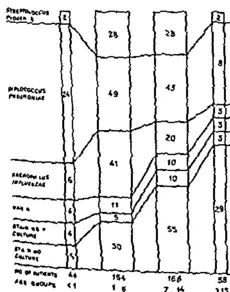


FIG 1 Aetiology of acute middle ear infection in different age groups

TABLE 5 *Polymicrobic specimens from acute middle ear infections*

Causative organisms	No of specimens
Haemoph infl + Staph aureus	1
Diploc pneum + Haemoph infl	12
Diploc pneum + Staph aureus	4
Streptoc pyog + Diploc pneum	2
Streptoc pyog + Haemoph parainfl	1
Streptoc viridans + Neisseria crassa	2
Staph aureus + Klebsiella	1
Staph albus + E coli	1
Diploc pneum + Haemoph infl + Staph aureus	1
Diploc pneum + Haemoph infl + Staph albus	1
Total	29

All the *Staph aureus* strains fermented mannitol, gave positive tests for coagulase and phosphatase, and produced α toxin

The frequencies of different types of pneumococci are given in Table 6 The incidence of the different pneumococcal types did not differ significantly in the various age groups

Fig 1 reveals that the incidence of pneumococci was approximately the same in all age groups Otitis of streptococcal origin, however, was more frequent in the age groups 2–6 and 7–14 years than in the group less than one year of age and in the groups over fifteen years of age The incidence of *H influenzae* was highest in the group 2–6 years The incidence of "non bacterial" otitis seems to increase with age of the patients No correlation

TABLE 6 *Type distribution of isolated Diplococcus pneumoniae strains*

Type	No of strains	%	Type	No of strains	%
I	39	25.5	XIII	1	
II	2		XIV	1	
III	17	11.1	XV	[illegible]	
IV	[illegible]		XVII	1	
V	1		XVIII	[illegible]	
VI	10	6.5	XIX	31	20.3
VII	9	5.9	XX	5	
VIII	[illegible]		XXIII	2	
IX	7		XXXIII	1	
X	1		XXXV	1	
XII	1				
			Total number of strains typed	153	

Various explanations have been proposed in recent papers for the existence of "non-bacterial" otitis. The many unsuccessful attempts to isolate viruses from middle ear exudates suggest that otitis media is rarely if ever caused by a virus. Our results speak against an assumption that at some stage of the infection, e.g. either at its beginning or end, the middle ear exudate is free of bacteria. Definite evidence has been collected which shows that defensive mechanisms effect the destruction of bacteria in middle ear exudates (Suirala 1957, Suirala *et al.* 1961).

On the basis of observed histopathological changes in the middle ear it has been concluded that viruses are important factors in acute middle ear infections (Shambaugh 1959), in that viral infection paves the way for bacterial infection. The significance of viruses is, however, strongly contradicted by the fact that we were unable to isolate viruses from any of the examined middle ear exudates, irrespective of whether the latter contained bacteria or not. The same is indicated by the results of studies of acute otitis during typical viral diseases in patients from whose middle ear exudates no viruses were isolated although, for example, influenzae virus A was isolated from simultaneously taken throat washings. The middle ear infections were typical monomicrobic infections caused by common respiratory pathogens (Kortekangas & Raunio 1959). With these statements we do not intend to deny the well known effects of viral infections on general resistance to bacterial infection.

As we found 15 cases among the 77 patients with bilateral otitis media in which the inflammation was bacterial in one ear and "non-bacterial" in the other, we are inclined to suspect that the diagnosis of "non-bacterial" otitis is very often due to the difficulty or *impossibility of detecting bacteria in middle ear exudates*. The reason may be the suppression of bacterial and probably also viral multiplication by defensive factors within the organ. The development and mode of action of these factors are still unsolved problems.

ZUSAMMENFASSUNG

563 Proben, während zwei *Perioden* (1956–57 und 1962–63) mittels des Saugpunktierverfahrens *von* Patienten mit akuter Mittelohrinfektion entnommen, wurden zwecks Feststellung von Mikroorganismen gezüchtet. Auch während der ersten Periode wurden virologische Methoden angewendet. Die Untersuchungen erwiesen, dass *Diplococcus pneumoniae, H. influenzae* und *Strept. pyogenes* noch immer die gewöhnlichsten Verursacher akuter Mittelohrinfektionen sind, und dass *Staph. aureus* von geringerer Bedeutung ist als bisher behauptet wurde. Die akute Mittelohrinfektion ist beinahe immer eine monomikrobische Infektion. Die angewendeten Verfahrungsweisen brachten weder PPL Organismen noch Viren an den Tag.

practically constant incidence whereas the incidence of streptococci decreased slightly and that of *H influenzae* increased in the later series The incidence of these species is however greatly dependent on epidemiological factors and may therefore be subject to wide variation

The results of our two series did not confirm the slight increase of the frequency of staphylococci found by Heikkila and Peltonen (1956) This may be due to the somewhat different method of transporting the specimens to the laboratory Hence *it seems that the incidence of staphylococci has not* increased during the period 1948–1963

A high incidence of *Staph aureus* as an aetiologic factor in acute middle ear infection has however been stressed in recent years (McNeill 1962 Mawson 1963) These results must be attributed to unsatisfactory techniques of taking specimens and in many cases defective bacteriologic techniques Although several investigators have clearly pointed out the unreliability of the swab technique of taking specimens from the middle ear (Lahikainen 1953 van Dishoeck *et al* 1959) results obtained using this technique have *nevertheless been reported in recent years The fairly frequent occurrence* of staphylococci in the specimens of our series that contained several bacterial species may however be due in many cases to contamination from the external meatus This view is supported by the fact that in these specimens the other bacterium always was a typical respiratory pathogen and evidently responsible for the infection If a residual acute middle ear infection before the organ has recovered from a previous infection is in question it seems from our own observations (Kortekangas & Gronroos) in agreement *with the* findings of Dishoeck *et al* (1959) that staphylococci occur in higher frequency in such infections than in primary acute cases also when specimens are removed by the puncture aspiration technique

Our series shows clearly that pneumococci *H influenzae* and streptococci are the aetiologic factors in four out of every five cases of acute otitis media These organisms apparently possess a greater affinity to the middle ear than other bacteria of the respiratory tract The high incidence of *H influenzae* in the group 2–6 years agrees with the variation of the antibody content and of the bactericidal effect of the blood against *H influenzae* at different ages (Fothergill & Wright 1933 Tunevall 1952)

The higher proportion of non bacterial otitis in our series as compared with series reported previously is in our view a consequence of our more realistic active approach to the problem We strove to collect middle ear fluids from all ears from which this was possible *even from those where* the signs of infection were very weak It is known that non bacterial otitis is *more* common in such cases than in cases where the signs and symptoms are severe this was observed also in our series Also the commonly employed swab technique must be responsible for the low proportion of non bacterial otitis in previously reported studies because it is difficult to obtain specimens uncontaminated durin

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EXPERIMENTAL STUDIES ON THE LOCAL EFFECTS OF ACETYLCHOLINE, ANTICHOLINERGIC SUBSTANCES AND CHOLINESTERASE INHIBITORS ON VESTIBULAR FUNCTION

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A study has been made of the effects of acetylcholine, anticholinergic substances (atropine, tetraethylammonium) and cholinesterase inhibitors (diisopropylfluorophosphate), introduced into the endolymphatic duct, on vestibular function The introduction of these substances into the endolymphatic duct was achieved by means of double fistulization of the lateral semicircular canal Electronystagmography was used to investigate the functional effects of this procedure From the findings obtained it seems possible to conclude that an accumulation of acetylcholine at the efferent nerve endings inhibits the transmission of afferent impulses, and that acetylcholine also takes part in the mechanism of transmission of nerve impulses from the neuroepithelial cell to the afferent fibre

INTRODUCTION AND SCOPE OF THE INVESTIGATION

The existence of a component of efferent fibres in the vestibular nerve originating in the medulla oblongata was recently demonstrated both anatomically (Petroff 1955 Rasmussen & Gacek, 1958 Carpenter, Bard & Alling 1959 Gacek 1960 Carpenter, 1960) and electrophysiologically (Sala 1962 Schmidt 1963)

The study of the efferent innervation of the vestibular receptors was begun systematically by Rossi (1960 1962) using histochemical and embryological methods and continued with anatomical methods by Rossi & Cortesina (1962*a* *b* 1963 1964)

This research was prompted by an observation made by Rossi in 1960, namely that the cochlear efferent fibres in the intraganglionic spiral bundle could be easily distinguished from the afferent fibres owing to their high acetylcholinesterase (AChE) content, evidenced in their positivity to the Koelle & Friedenwald reaction (1949)

Rossi decided to determine whether or not the afferent and efferent components of the vestibular nerve also showed a difference in response to the Koelle and Friedenwald AChE test

Employing anatomical histochemical and experimental methods Rossi & Cortesina (1962*a* *b* 1963 1964) were able to demonstrate in the guinea pig

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Buongiovanni, Cortesina & Voena 1964) on the effects of the intracarotid injection of diisopropylfluorophosphate (DFP)—a cholinesterase inhibitor—on vestibular function Rabbits were chosen for this study as they had been found by Rossi & Cortesina (1964) to possess a vestibular efferent fibre system similar to that observed in guinea pigs (Rossi & Cortesina 1962 a, b 1963) Intracarotid injection of DFP was found to produce the vestibular syndrome described in 1949 by Freedman & Himwich and termed by them adversive syndrome

Histochemical investigation employing Koelle and Friedenwald's AChE test demonstrated the disappearance of positivity to this test in the efferent vestibular fibres and ampullary receptors ipsilateral to the common carotid into which DFP was injected Without ruling out the possibility of other mechanisms it would seem that the pathogenesis of the vestibular syndrome elicited by intracarotid DFP injection is at least partly related to a reduction in the quantity of acetylcholinesterase and a resultant increase in the *quantity* of acetylcholine which occur under the above experimental conditions in the efferent vestibular fibres and neuroepithelium of the ampullary crests

With the intracarotid route of administration employed in these preliminary experiments the DFP naturally reaches many anatomical structures It was therefore not possible to determine precisely the functional effects of DFP on the ampullary receptors alone

For this reason a study of the direct action of DFP on the ampullary receptors was thought necessary It was also decided to study the effects of acetylcholine and anticholinergic substances (atropine, *tetraethylammonium*) so as to obtain a series of functional findings closely related in some cases to an accumulation of acetylcholine (experiments with DFP and *acetylcholine*) and in others to the inhibition of acetylcholine at the ampullary receptors (experiments with atropine and tetraethylammonium)

MATERIALS AND METHODS

Eighty two rabbits were employed in the experiments The functional effects of the substances used *in the investigation* were recorded by means of Tonnies electronystagmographic apparatus (consisting of a two channel nystagmograph and an electrically controlled rotating chair) Electrodes implanted in the periorbital subcutaneous tissue according to Aschan Bergstedt & Stahle's technique (19[illegible]) *were used to record* the potentials

Under local anaesthesia (1 per cent xylocaine) the left lateral semicircular canal was exposed through the retroauricular route Care was taken to preserve intact the *middle ear structures* At this stage the animal was subjected to clockwise and anticlockwise rotation (with covered head) in order to test nystagmic response while the labyrinths were still intact (acceleration [illegible] sec², terminal velocity 110°/sec sudden arrest) With a small file a fistula was made in the left lateral semicircular canal as distally as possible from the ampulla A *dissecting* microscope was used throughout the procedure Once the nystagmus caused by the creation of this *fistula*

and rabbit the existence of two bundles of efferent fibres to the ampullary receptors and to establish for the first time their origin, course and relations.

The *first* of these two bundles arises in a small nucleus termed by Rossi and Cortesina, who were the first to demonstrate its existence, *interposed vestibular nucleus*. Situated dorsally and medially to the cranial end of the inferior vestibular nucleus and ventrally to the caudal end of the lateral vestibular nucleus, the *interposed vestibular nucleus* cannot be morphologically identified with either the four main vestibular nuclei or the other known cell groups topographically related to the main nuclei. It is composed, in the guinea pig, of between 120 and 150 cells and gives rise to a bundle of efferent fibres termed by Rossi & Cortesina (1962*a*, *b*, 1963) *direct ventral efferent vestibular bundle*.

The second bundle of efferent fibres to the vestibular receptors arises in cells situated in the ventral portion of the caudalmost tract of the lateral vestibular nucleus. This bundle of nerve fibres, whose origin and course were first demonstrated by Rossi & Cortesina (1962*a*, *b*, 1963, 1964), is the *direct dorsal efferent vestibular bundle*.

Rossi & Cortesina's studies (1962*a*, *b*, 1963, 1964) showed that the efferent connexions of the vestibular receptors also comprise a component of fibres arising from cells in the bulbar and pontine reticular formation near the median raphe (*direct reticulo-cochlear and vestibular bundle*). No evidence was obtained of the existence of crossed efferent fibres to the vestibular receptors.

Finally, Rossi & Cortesina (1962*a*, *b*, 1963, 1964) were able to confirm Ireland & Farkashidy's finding (1961) that the acetylcholinesterase activity observed at the vestibular receptors belongs to the nerve endings of the efferent fibres. Sagittal section at the lateral angle of the fourth ventricle was found to bring about the disappearance of acetylcholinesterase activity at the macular and ampullary receptors.

In recent years considerable research on subsidiary aspects of this subject has been made, partly at a submicroscopic level (Wersäll, 1954, 1956; Smith, 1956; Engström, 1958; Wersäll, 1960; Hilding & Wersäll, 1962) and partly by histochemical means (Dohlman, Farkashidy & Salonna, 1958; Ireland & Farkashidy, 1961). On the strength of the findings of this research it can be deduced *that the nerve endings of the efferent fibres are situated* at the base of the neuroepithelial cells, both type I and type II, of the ampullary crests, that they contain large amounts of acetylcholinesterase, and that this enzyme is only found if the efferent vestibular fibres are intact.

The presence of acetylcholinesterase at a well defined point in the complex constituted by the ampullary receptor, afferent fibre and efferent fibre implies the existence at this point of a chemical nervous impulse transmission mechanism acting through an acetylcholine-cholineacetylase-acetylcholinesterase system governed by the *efferent fibres*.

This supposed situation formed the basis of a preliminary study (Rossi

In this group of experiments 20 rabbits of the same breed were used. The weights ranged from 1.3 to 1.6 kg. In all the animals horizontal rotatory nystagmus followed the opening of both the fistula distal to the ampulla of the left lateral semicircular canal and that proximal to the ampulla of the left lateral semicircular canal. Duration of nystagmus, of which the rapid component was to the left, ranged from 38 to 105 seconds.

Subsequent rotation to the right was followed by a nystagmic response of far smaller proportions than that observed before opening the two fistulae. Rotation to the left also elicited a greatly reduced nystagmic response compared with that obtained before opening the two fistulae, the values being almost the same as those noted for rotation to the right. More will be said about the importance of this finding in a later paragraph.

The introduction of the DFP solution into the fistula proximal to the ampulla, by the method described above, resulted in the appearance, after an interval varying between 3 and 18 seconds, of a horizontal rotatory nystagmus, whose rapid component was to the right, that is in a direction away from the side of the labyrinth operated on. The duration of this nystagmus ranged from 1 min 35 sec to 9 min 38 sec.

Rotation to the right 15 min after cessation of the nystagmus caused by DFP administration elicited a nystagmic response of even smaller proportions than that observed after opening the two fistulae. It should be noted that once again rotation to the left gave the same values as obtained with rotation to the right.

A further rotation to the right and left was performed 90 min after cessation of the nystagmus caused by DFP administration. In this case the nystagmic response was almost the same for both right and left rotation and pointed to the recovery of vestibular reflex function generally to values intermediate between those recorded before the experiment and those recorded after opening the two fistulae.

The findings of one of the experiments are incorporated in Fig. 1, which shows the intervals between the various stages of the experiment.

[illegible] values recorded on applying the rotation test after opening the two fistulae and before administering the DFP. Rotation to the left was also followed by a reduced nystagmic response compared with that elicited by the rotation test immediately after opening the two fistulae. [illegible]

[illegible] recorded after opening the two fistulae.

The four rabbits were subjected to histochemical analysis. Rabbits 7 and 13 were sacrificed during the nystagmus caused by DFP administration. Rabbits 4 and 20 were sacrificed 90 min after cessation of this nystagmus. In rabbits 7 and 13 Koelle and Friedenwald's AChE test was positive at the ampullary crest of the right lateral semicircular canal and negative at the ampullary crest of the left lateral semicircular canal (Fig. 2 A and B). In rabbits 4 and 20 Koelle and Friedenwald's AChE test was positive on both sides.

Experiments with Acetylcholine Chloride

100 mg of acetylcholine chloride was dissolved in 10 ml of saline and a 0.0125 ml aliquot containing 125 µg of acetylcholine chloride was taken.

had ceased and after a suitable interval a second fistula was made by the same technique proximal to the ampulla. As before, the ensuing nystagmus was allowed to cease before proceeding with the experiment. The animal was then subjected to right and left rotation according to the technique described above.

A small plasticine support was placed between the two fistulae so as to create a small cavity around the fistula proximal to the ampulla. The test substance was allowed to run from a micropipette and collect in this cavity. The ensuing nystagmic response was then carefully recorded. At 15 minutes and 90 minutes after cessation of nystagmus the animal was subjected to right and left rotation according to the usual technique.

The double fistulization procedure was adopted after a series of preliminary studies in which small quantities of methylene blue were added to the same substances (in the same concentrations) as were used in the under-mentioned experiments. To verify that the substance had reached the endolymph, a segment of the membranous semicircular canal was isolated and sections made from it with the freezing microtome. If the inner lining epithelium of the membranous semicircular canal was seen to be stained, it could be safely assumed that the test substance had reached the endolymph. With only one fistula in the lateral semicircular canal, the dynamic effects of the test substances and the vital staining of the methylene blue were almost nil. On the contrary, with two fistulae in the lateral semicircular canal, highly significant dynamic effects were observed, accompanied in all cases by vital staining of the inner lining epithelium of the membranous semicircular canal.

The validity of each of the experiments was verified by a series of control tests employing only the solvent of each of the test substances. Since these control tests were negative, it could be concluded that the phenomena observed in the various groups of experiments were due exclusively to the action of the test substances.

In some of the animals a histological examination was made of the ampullary crests of the left lateral semicircular canal and, for control purposes, of the right lateral semicircular canal. Haematoxylin-eosin staining was used for histological examination in the experiments with acetylcholine, atropine and tetraethylammonium. In the experiments with DFP, Koelle & Friedenwald's AChE test (1949) modified by Holmstedt (1957 *a*, *b*) was also used for histological examination following decalcification of the petrosa with EDTA.

RESULTS

Experiments with Diisopropylfluorophosphate (DFP)

From a stock solution of DFP in propylene glycol a 0.1 ml aliquot containing 10 mg of DFP was taken and made up to 10 ml with saline. With a micropipette 0.0125 ml containing 12.5 μg of DFP was aspirated and allowed to run down one of the sides of the small cavity made with plasticine around the fistula proximal to the ampulla of the left lateral semicircular canal.

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The findings of one of the experiments are incorporated in Fig 1, which shows *the intervals between the various stages of the experiment*

In 4 cases (rabbits 5, 9, 11 and 18) DFP *administration did* not cause nystagmus Rotation to the right, performed after 3 min, showed a fall in the reflex action of the left labyrinth compared with the values *recorded on* applying the rotation test after opening the two fistulae and before *administering* the DFP Rotation to the left was also followed by a reduced *nystagmic response* compared with that elicited by the rotation test immediately *after opening* the two fistulae Checks made at 15 and 90 min after a[illegible]

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From a stock solution of DFP in propylene glycol a 0.1 ml aliquot containing 10 mg of DFP was taken and made up to 10 ml with saline. With a micropipette 0.0125 ml containing 12.5 μg of DFP was aspirated and allowed to run down one of the sides of the small cavity made with plasticine around the fistula proximal to the ampulla of the left lateral semicircular canal.

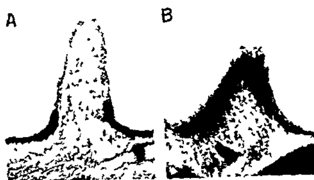


Fig 2 Rabbit No 7 The animal was sacrificed during nystagmus induced by diisopropylfluorophosphate (DFP) introduced into the left lateral semicircular canal *A*—Ampullary crest of the left lateral semicircular canal The Koelle and Friedenwald acetylcholinesterase test is negative at the neuroepithelium *B*—Ampullary crest of the right lateral semicircular canal The Koelle and Friedenwald acetylcholinesterase test is positive at the neuroepithelium Koelle and Friedenwald [illegible]

In this group of experiments 18 rabbits of the same breed were used Their weights ranged from 1 3 to 1 6 kg

The opening of each of the two fistulae in the left lateral semicircular canal was followed by a horizontal rotatory nystagmus lasting between 28 and 90 sec The rapid component was to the left

Rotation to the right showed a reduction in the reflex function of the left labyrinth compared with the control values obtained before the experiment This was accompanied by a similar fall in reflex function in the contralateral labyrinth

The introduction of acetylcholine chloride into the left lateral semicircular canal resulted in the appearance, after an interval varying between 3 and 21 sec, of a horizontal rotatory nystagmus, whose rapid component was to the right and which lasted between 1 min 30 sec and 13 min 40 sec

Rotation 15 min after cessation of this nystagmus produced a nystagmic response presenting even lower values in both left and right labyrinth, than were recorded with the rotation test applied immediately after opening the two fistulae

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at 1 hr [illegible] min *I* rotation to the right duration of post rotatory nystagmus 4 sec average rate of movements 3 per sec average amplitude of movements 11 [illegible]

at 1 hr [illegible] min *J* rotation to the left duration of post rotatory nystagmus 7 sec average rate of movements 2 3 per sec average amplitude of movements 15

at 1 hr [illegible] min *C* introduction of DFP (arrow) after 7 sec horizontal rotatory nystagmus to the right duration of nystagmus [illegible] min 43 sec

at [illegible] hr 1[illegible] min *H* rotation to the right duration of post rotatory nystagmus 2 sec average rate of movements 2 per sec average amplitude of movements 7 30

at [illegible] hr [illegible] min *I* rotation to the left duration of post rotatory nystagmus 5 sec average rate of movements 2 per sec average amplitude of movements 9 22

at 3 hr [illegible] min *J* rotation to the right duration of post rotatory nystagmus 12 sec average rate of movements 3 8 per sec average amplitude of movements 9°22

at 3 hr 10 min *M* rotation to the left duration of post rotatory nystagmus 17 sec average rate of movements 3 [illegible] per sec average amplitude of movements 11°

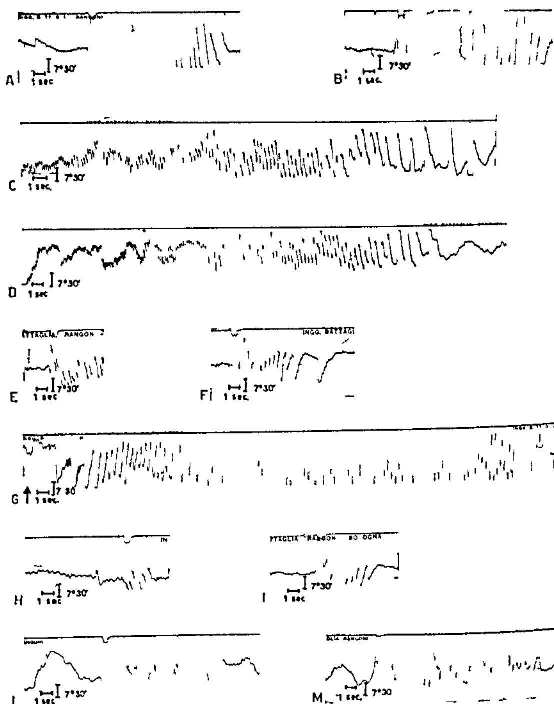


Fig 1 Experiment No 8 with diisopropylfluorophosphate [illegible]

Stages of the experiment

A—rotation to the right duration of post rotatory nystagmus 13 sec average rate of movements 2 1 per sec average amplitude of movements 18 1?

at 10 min B—rotation to the left duration of post rotatory nystagmus 1? sec average rate of movements 2 2 per sec average amplitude of movements 18 15

at 50 min C—creation of first fistula onset of horizontal rotatory nystagmus to the left duration of nystagmus 46 sec

at 1 hr 5 min D—creation of second fistula onset of horizontal rotatory nystagmus to the left duration of nystagmus 12 sec

Rotation 90 min after cessation of the nystagmus caused by the administration of acetylcholine chloride elicited a nystagmic response of almost equal proportions in both right and left rotation tests This pointed to a recovery of vestibular reflex activity generally to values intermediate between those recorded before the experiment and those recorded after opening the two fistulae

In 3 cases (rabbits 22 28 and 30) acetylcholine chloride did not cause nystagmus, but only a reduction in the nystagmic response of the left labyrinth to the rotation test performed after 3 min compared with that elicited immediately after opening the two fistulae A corresponding reduction in reflectivity was noted in the contralateral labyrinth

Tests performed after 15 and 90 min showed a gradual return of reflectivity in the two labyrinths to values intermediate between those recorded before the experiment and those recorded after opening the two fistulae

Two rabbits (rabbits 25 and 29) were subjected to histological examination by means of haematoxylin eosin staining Rabbit 25 was sacrificed during the nystagmus caused by acetylcholine chloride administration Rabbit 29 was sacrificed 90 min after cessation of this nystagmus The histological sections showed no appreciable changes in the ampullary crest of the left lateral semicircular canal

Experiments with Tetraethylammonium Chloride

100 mg of tetraethylammonium chloride was dissolved in 10 ml of saline and a 0 0125 ml aliquot containing 125 μg of tetraethylammonium chloride was taken

In this group of experiments 14 rabbits of the same breed were used Their weights ranged from 1 3 to 1 6 kg

The opening of each of the two fistulae in the left lateral semicircular canal was followed by a horizontal rotatory nystagmus whose rapid component [illegible]

[illegible] in the values recorded before the experiment There was a corresponding reduction in reflectivity in the right labyrinth

The introduction of tetraethylammonium chloride into the left lateral semicircular canal did not cause nystagmus in any of the 14 animals used in this group of experiments

Rotation tests performed 3 and 90 min after the administration of tetraethylammonium chloride showed no change in the reflex activity of the right and left labyrinths compared with the values obtained before the opening of th[illegible] the [illegible]

[illegible] inter[illegible] experiment

Histological examination was done in 2 rabbits (rabbits 60 and 64) with haematoxylin eosin staining Both animals were sacrificed 5 min after the introduction of tetraethylammonium chloride

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at 3 hr [illegible] min [illegible] rotation to the right duration of post rotatory nystagmus 10 sec average rate of movements 4 per sec average amplitude of movements [illegible]
at 3 hr [illegible] min [illegible] rotation to the left duration of post-rotatory nystagmus [illegible] sec average rate of movements 4 per sec average amplitude of movements [illegible]

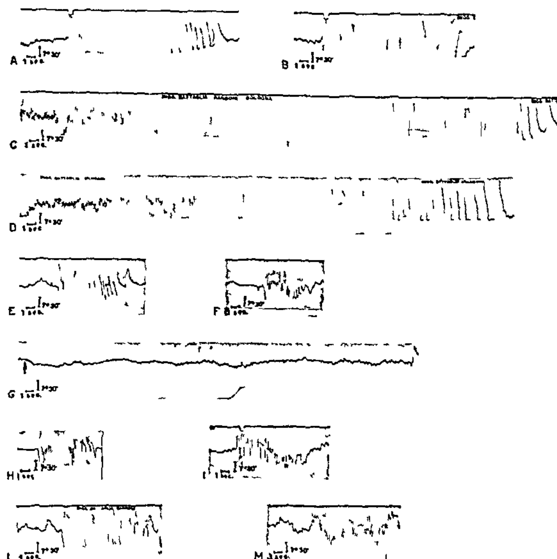


Fig. 3. Experiment No. 41 with tetraethylammonium chloride. Labyrinth operated on: left.

Stages of the experiment

A—rotation to the right: duration of post-rotatory nystagmus 14 sec; average rate of movements 3.3 per sec; average amplitude of movements 20°.
at 10 min *B*: rotation to the left: duration of post-rotatory nystagmus 14 sec; average rate of movements 3.3 per sec; average amplitude of movements 22°30'.
at 1 hr 5 min *C*: creation of first fistula: onset of horizontal rotatory nystagmus to the left; duration of nystagmus 64 sec.
at 1 hr 20 min *D*: creation of second fistula: onset of horizontal rotatory nystagmus to the left; duration of nystagmus 60 sec.
at 1 hr 35 min *E*—rotation to the right: duration of post-rotatory nystagmus [illegible] sec; average rate of movements 3 per sec; average amplitude of movements 1[illegible].
at 1 hr 15 min *F*: rotation to the left: duration of post-rotatory nystagmus [illegible] sec; average rate of movements 3.6 per sec; average amplitude of movements 12°10'.
at 2 hr *G*—introduction of tetraethylammonium chloride: no demonstrable effect.
at 2 hr 3 min *H*—rotation to the right: duration of post-rotatory nystagmus 7 sec; average rate of movements 3.7 per sec; average amplitude of movements 17°30'.
at 2 hr 13 min *I*—rotation to the left: duration of post-rotatory nystagmus 8 sec; average rate of movements 3.5 per sec; average amplitude of movements 15°.

The histological sections showed no appreciable changes in the ampullary crest of the left lateral semicircular canal

Experiments with Atropine Sulphate

100 mg of atropine sulphate was dissolved in 10 ml of saline and a 0 0125 ml aliquot, containing 125 μg of atropine sulphate, was taken

In this group of experiments 15 rabbits of the same breed were used Their weights ranged from 1 3 to 1 6 kg

The opening of each of the two fistulae in the left lateral semicircular canal was followed by a horizontal rotatory nystagmus, whose rapid component was to the left and which lasted between 37 and 103 sec

Rotation to the right showed a reduction in the reflex activity of the left labyrinth compared with the values recorded before the experiment There was a corresponding reduction in the reflex activity of the right labyrinth

The introduction of atropine sulphate into the left lateral semicircular canal resulted in the appearance, after an interval varying between 2 and 9 sec, of a horizontal rotatory nystagmus, whose rapid component was to the right and which lasted between 4 min 35 sec and 16 min 15 sec

Rotation tests performed 15 min after cessation of this nystagmus elicited a nystagmic response presenting values lower, in both left and right labyrinths, than those recorded during the rotation test applied immediately after opening the two fistulae

At 90 min from cessation of the nystagmus caused by introduction of atropine sulphate, the nystagmic response was almost the same in both right and left rotations This pointed to a recovery of vestibular reflex activity to values intermediate between those recorded before the experiment and those recorded after opening the two fistulae

The findings of one of the experiments are incorporated in Fig 4, which shows the intervals between the various stages of the experiment

In 4 cases (rabbits 70, 74, 76 and 80), atropine sulphate did not cause horizontal-rotatory nystagmus but simply a reduction in the nystagmic response of the left labyrinth to rotation after 3 min, compared with the values recorded immediately after opening the two fistulae There was a corresponding reduction in the reflex activity of the right labyrinth

Rotation tests performed after 15 and 90 min showed a gradual return of reflex activity of the left and right labyrinths to values intermediate between those recorded before the experiment and those recorded immediately after the opening of the two fistulae in the left lateral semicircular canal

Histological examination was done in 2 cases (rabbits 72 and 81) with haematoxylin eosin staining Rabbit 72 was sacrificed during the nystagmus caused by atropine sulphate administration Rabbit 81 was sacrificed 90 min after cessation of this nystagmus

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at 2 hr 20 min I—rotation to the left duration of [illegible] 8 sec , average rate of movements 2 [illegible]

at 3 hr 25 min I [illegible] 9 sec, average rate of movements 3 [illegible] average amplitude of movements 17°30

at 3 hr 35 min II—rotation to the left duration of post rotatory nystagmus 9 sec, average rate of movements 4 per sec average amplitude of movements 2[illegible]

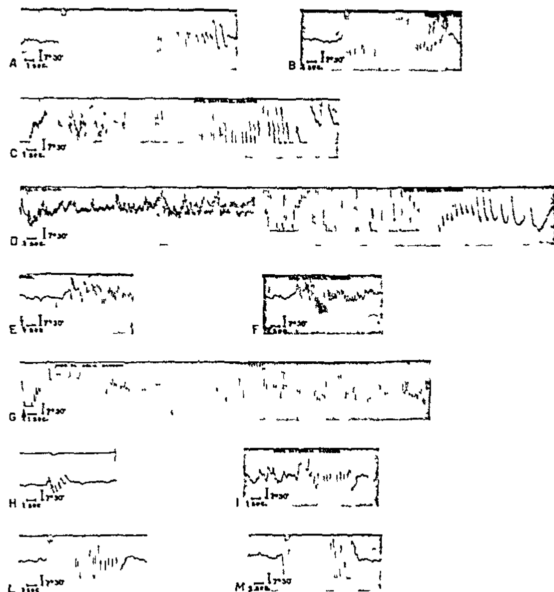


Fig. 4. Experiment No. 65 with atropine sulphate. Labyrinth operated on left.

Stages of the experiment

A—rotation to the right: duration of post rotatory nystagmus 20 sec, average rate of movements 3 per sec, average amplitude of movements 17–30°

at 10 min B—rotation to the left: duration of post rotatory nystagmus 14 sec, average rate of movements 3 per sec, average amplitude of movements 25°

at 55 min C—creation of first fistula: onset of horizontal rotatory nystagmus to the left, duration of nystagmus 36 sec

at 1 hr 10 min D—creation of second fistula: onset of horizontal rotatory nystagmus to the left, duration of nystagmus [illegible]2 sec

at 1 hr 25 min E—rotation to the right: duration of post rotatory nystagmus 7 sec, average rate of movements 4 per sec, average amplitude of movements 10

at 1 hr 3[illegible] min F—rotation to the left: duration of post rotatory nystagmus 8 sec, average rate of movements 4 per sec, average amplitude of movements 12

at 1 hr 50 min G—introduction of atropine sulphate (arrow): after 1 s[illegible] onset of horizontal rotatory nystagmus to the right, duration of nystagmus 5 min 25 s

at 2 hr 10 min H—rotation to the right: duration of post rotatory nystagmus 3 sec, average rate of movements 2 per sec, average amplitude of movements 6°

The histological sections showed no appreciable changes in the ampullary crest of the left lateral semicircular canal

Experiments with Atropine Sulphate

100 mg of atropine sulphate was dissolved in 10 ml of saline and a 0 0125 ml aliquot, containing 125 µg of atropine sulphate, was taken

In this group of experiments 15 rabbits of the same breed were used Their weights ranged from 1 3 to 1 6 kg

The opening of each of the two fistulae in the left lateral semicircular canal was followed by a horizontal rotatory nystagmus, whose rapid component was to the *left* and which lasted between 37 and 103 sec

Rotation to the right showed a reduction in the reflex activity of the left labyrinth compared with the values recorded before the experiment There was a corresponding reduction in the reflex activity of the right labyrinth

The introduction of atropine sulphate into the left lateral semicircular canal resulted in the appearance, after an interval varying between 2 and 9 sec, of a horizontal rotatory nystagmus, whose rapid component was *to the right and which lasted* between 4 min 35 sec and 16 min 45 sec

Rotation tests performed 15 min after cessation of this nystagmus elicited a nystagmic response presenting values lower, in both left and right labyrinths, than those recorded during the rotation test applied immediately after opening the two fistulae

At 90 min from cessation of the nystagmus caused by introduction of atropine sulphate, the nystagmic response was almost the same in both right and left *rotations* This pointed to a recovery of vestibular reflex activity to values *intermediate between* those recorded *before the experiment* and those recorded after opening the two fistulae

The findings of one of the experiments are incorporated in Fig 4, which shows the intervals between the various stages of the experiment

In 4 cases (rabbits 70 74, 76 and 80), atropine sulphate did not cause horizontal rotatory nystagmus but simply a reduction in the nystagmic response of the left labyrinth to *rotation* after 3 min, compared with the values recorded immediately after opening the *two fistulae* There was a corresponding reduction in the reflex activity of the right *labyrinth*

Rotation tests performed after 15 and 90 min showed a gradual return of reflex activity of *the left* and right labyrinths to values intermediate between those recorded before the *experiment* and those recorded immediately after the opening of the two fistulae *in the left lateral* semicircular canal

Histological examination was done in 2 cases (*rabbits 72 and 81*) with haematoxylin eosin staining Rabbit 72 was sacrificed during the nystagmus caused by atropine *sulphate* administration Rabbit 81 was sacrificed 90 min after *cessation* of this nystagmus

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at 2 hr 20 min *I*—rotation to the left duration of post rotatory [illegible]
of m[illegible]

at [illegible]

at 3 hr 35 mi[illegible]
of n oveme[illegible]

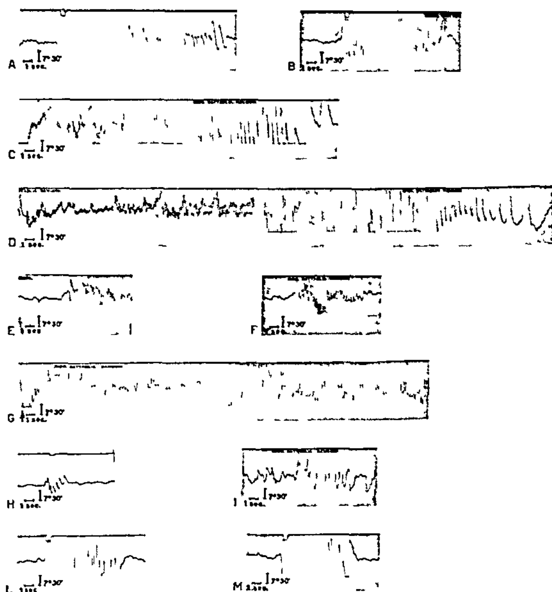


Fig. 4. Experiment No. 6, with atropine sulphate. Labyrinth operated on: left.

Stages of the experiment

A—rotation to the right: duration of post-rotatory nystagmus 20 sec; average rate of movements 3 per sec; average amplitude of movements 17°30'

at 10 min B—rotation to the left: duration of post-rotatory nystagmus 14 sec; average rate of movements 3 per sec; average amplitude of movements 25°

at 55 min C—creation of first fistula: onset of horizontal rotatory nystagmus to the left; duration of nystagmus 30 sec

at 1 hr 10 min D—creation of second fistula: onset of horizontal rotatory nystagmus to the left; *duration of nystagmus* 42 sec

at 1 hr 25 min E—rotation to the right: duration of post-rotatory nystagmus 7 sec; average rate of movements 4 per sec; average amplitude of movements 10°

at 1 hr 35 min F—rotation to the left: duration of post-rotatory nystagmus 8 sec; average rate of movements 4 per sec; average amplitude of movements 12°

at 1 hr 50 min G—introduction of atropine sulphate (arrow): after 1 sec onset of horizontal rotatory nystagmus *to the right*; duration of nystagmus 5 min 25 sec

at 2 hr 10 min H—rotation to the right: duration of post-rotatory nystagmus 3 sec; average rate of movements 2 per sec; average amplitude of movements 6°

followed, within 90 min by the restoration of the reflectivity levels recorded immediately before introduction of each of the substances

Interpretation of the findings of the above experiments is difficult for the following reasons

1 It is not possible to determine exactly how much of the test substance acts on the neuroepithelium

2 Certain of the substances may cause different effects according to the quantity used

3 It cannot be ruled out that certain of the substances used in the above experiments may act not only on nervous impulse transmission but also through a direct pharmacodynamic mechanism

Notwithstanding these reservations there is reason to suppose that in the experiments with acetylcholine there was an accumulation of this substance throughout the receptor/afferent fibre/efferent fibre system *Functionally*, the accumulation of acetylcholine corresponds to the appearance of a horizontal rotatory nystagmus the rapid component of which is in the direction of the labyrinth contralateral to that subjected to acetylcholine accumulation

We believe that this functional effect is the result of a severe imbalance between the right and left vestibular systems following a complete unilateral block or a marked unilateral reduction in the transmission of impulses in resting conditions from the ampullary crests to the brain centres (*Lowenstein & Sand* 1936 Gernandt 1949 Ledoux, 1949)

The experiments with acetylcholine provide no evidence *of the exact point in the* receptor/afferent fibre system at which this inhibition *of afferent* impulse transmission takes place

In the experiments *with DFP there* was an accumulation of acetylcholine theoretically *confined to* the synapse between the efferent fibre and the receptor/afferent fibre *system*

The functional effects observed in these experiments can also be regarded *as the result of a severe functional* imbalance *between the right and left* vestibular system through the above mentioned *mechanism*

The large quantities of acetylcholinesterase *contained* in the nerve endings of the efferent fibres and *the nature* of the synaptic linkages they form with the receptor/afferent *fibre system* suggest that the inh[illegible]
p[illegible]
in[illegible]
a[illegible] [illegible]not be exactly identified but which undoubtedly form part of the receptor/afferent fibre system

The particular site of acetylcholine accumulation in the above *experiments* suggests that under physiological *conditions the efferent fibres* release acetylcholine at this site and thereby *control the transmission of afferent impulses*

The histological sections showed no appreciable changes in the ampullary crest of the left lateral semicircular canal.

Control Experiments with the Solvents of the Substances used in the above Experiments

The introduction of 0.0125 ml of saline or of a solution containing 0.1 ml of propylene glycol and 9.9 ml of saline did not cause nystagmus nor any variation in the reflex activity of the left labyrinth from values recorded after opening the two fistulae.

The control experiments with saline were performed in 8 rabbits, those with propylene glycol diluted in saline in 7 rabbits. The results were the same in all these animals.

COMMENT AND CONCLUSIONS

The purpose of the present paper has been to illustrate the objectives and findings of a series of experiments in rabbits in which the ampullary receptors of the left lateral semicircular canal were exposed to the action of acetylcholine, an anticholinesterase substance (DI P), an anticholinergic specific for ganglionic receptors (tetraethylammonium) and an anticholinergic specific for post-ganglionic receptors (atropine).

In the experiments with acetylcholine and DI P the object was to study the effects of an accumulation of acetylcholine, directly or indirectly induced, on ampullary receptor function.

In the experiments with atropine and tetraethylammonium the object was to identify the site of acetylcholine under physiological conditions by blocking its effects.

The test substances were introduced through two fistulae made in the left lateral semicircular canal. It should be noted that the opening of these fistulae caused a reduction in the nystagmic response of the left labyrinth to the rotation test together with a corresponding reduction in the nystagmic response of the right labyrinth to the rotation test. Similarly, the subsequent further reduction in reflex activity of the left labyrinth induced by the test substance and its return to near pre-experiment values were in all cases accompanied by corresponding changes in the reflex activity of the right labyrinth.

In the experiments with acetylcholine and DI P electronystagmographic recording provided evidence that an accumulation of acetylcholine at the receptor/afferent fibre-efferent fibre system causes, in most cases, a horizontal rotatory nystagmus whose rapid component is in the direction opposite to the side of the labyrinth operated on. In a small percentage of cases the introduction of the substance did not bring about nystagmus but simply a reduction in the reflex activity of the left labyrinth accompanied by a corresponding reduction in the reflex activity of the right labyrinth.

Similar findings were obtained in the experiments with atropine. Tetraethylammonium, however, was found to have no effect.

The effects of acetylcholine, DI P and atropine were transitory and were

pothesis that this vestibular *interdependence* is governed by the activity of the efferent vestibular fibres

Further investigation should verify the validity or otherwise of the lines of reasoning on which the above conclusions are based Throughout the experiments described in the present paper we followed a theoretical and experimental approach believed to be unique in the study of this subject

RÉSUMÉ

Les auteurs ont étudié les effets produits sur la fonction vestibulaire du lapin par l introduction dans l endolymphe d acétylcholine de composés anticholinergiques (atropine tetraethylammonium) et de substances pourvues d activité anticholinestera sique (diisopropylfluorophosphate) L introduction dans l endolymphe de ces substances a été obtenue par une double fenestration du *canal semi-circulaire latéral* et l étude fonctionnelle a eté accomplie par enregistrement électronystagmographique A travers ces expériences il parait possible déduire qu une accumulation d acétylcholine à niveau des expansions synaptiques efférentes empeche la *transmission* des impulsions afférentes et que l acetylcholine prend part aussi au mécanisme de la transmission de l impulsion nerveuse de la cellule ciliee à la fibre afférente

ZUSAMMENFASSUNG

Die Autoren haben die Wirkungen auf die Vorhoffunktion studiert *die durch die* Einfuhrung von Azetylcholin von *anticholinergischen Stoffen* (Atropin Tetraaethyl *Ammonium*) *und* von anticholinesterasischen Stoffen (diisopropyl*fluorphosphat*) in die Endolymphe gefordert werden Die Einfuhrung dieser Stoffe in die Endolymphe wurde durch eine doppelte *Fensterung des Halbrunden* Seitengefasses erreicht und *das Funktionsstudium wurde durch* elektronystagmographische Aufnahme ausgefuhrt Aus den Ergebnissen dieser Forschungen folgt dass eine Anhaufung *von Azetylcholin* in den herausfuhrenden *Nervenendungen* die Ubertragung der herein fuhrenden Impulse hemmt und dass das Azetylcholin am Ubertragungsmechanismus des Nervenimpuls *von der Neuroep*ithelzelle zur hereinfuhrenden Faser beteiligt ist

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Tetraethylammonium did not have any functional effect in any of the laboratory animals used.

In the experiments with atropine the functional effects may also be thought to result from a severe imbalance between the right and left vestibular systems consequent upon a complete unilateral block or a marked unilateral reduction in afferent impulse transmission.

The findings of the experiments with atropine and the apparently paradoxical finding of identical functional effects in the experiments with atropine and those involving acetylcholine accumulation seem to suggest that acetylcholine plays a part in the mechanism of transmission of nerve impulses from the receptor to the afferent fibre.

If acetylcholine exerted its action only at the *synapse between efferent* fibre and receptor/afferent fibre system the functional effects would not have been as observed for atropine would block only the efferent impulses.

There thus seems to be good reason to assume that in physiological conditions acetylcholine plays a part at the level of the labyrinthine neuroepithelium in the mechanism underlying afferent impulse transmission and control.

As already mentioned certain animals both in the experiments with acetylcholine and in those with DFP and atropine did not exhibit horizontal rotatory nystagmus but simply a reduction in reflectivity of the labyrinth operated on. This we feel is the expression not so much of a qualitative difference in the actions of the various substances used but rather of a quantitative difference probably related to the amount of substance which manages to reach the vestibular receptors.

It would appear that in such cases the conditions for the development of an imbalance between the right and left vestibular system of such proportions as to cause nystagmus are not created whereas in the cases in which the vestibular system of one side predominates markedly over that of the other side nystagmus occurs.

It should finally be noted that in all our experiments the reduction in post-rotatory nystagmus induced by double fistulization of the left lateral semicircular canal was accompanied by a corresponding reduction in the nystagmic response of the right labyrinth. Similarly the further reduction in left labyrinth reflectivity caused by the administration of the substances used in the investigation and the subsequent recovery of left vestibular reflectivity to near pre-experiment levels were in all cases accompanied by corresponding changes in the nystagmic response of the right labyrinth.

These signs of *vestibular interdependence* observed in all the experiments described above seem to reflect an attempt by the body to maintain, within certain limits, the equilibrium between the two systems which under physiological conditions function in perfect harmony. We would advance the hy

ON SOME HISTOCHEMICAL ASPECTS OF THE OTOSCLEROTIC FOCUS

State and Significance of the Sulfhydril Groups

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The demonstration of sulfhydril groups in the region of the *otospongious focus* during the course of the first stages of their evolution seems to us to be of a twofold interest. They indicate a proteolytic activity in the region of the fundamental substance in the bone and equally constitute a characteristic trait in the histochemical field of the first stages of the disease.

The scarcity of the operative material has long prevented any histochemical study of the otosclerotic focus. Now that the microsurgery of the stapes (derived from Dr. Shea's technic) is widely used this major difficulty has disappeared and the near future will certainly be a time of widespread studies in this field, this in spite of many difficulties that remain to be solved.

These are bound to the evolution of the otosclerotic disease *and to its* specific bony location. Besides there are many evidences in the field of histoenzymology of many enzymes short acting life: these short lasting enzymes disappear rapidly from their cellular or histological site of activity. So they may be partly responsible for the complexity of the remodellings observed along the protracted *course* of the otosclerotic disease. These facts result in the *necessity of studying* a great number of different operative material. This material must be collected aseptically, *stored* as shortly as possible in the deep freezer and all samples studied under the same optimal conditions to yield comparative results. *Nevertheless* the necessary controls appear particularly difficult to establish, as a rule each histological or enzymological research needs the whole of the dissected, usually fragmented platina. This is why controls of each worker's results by others in the same field are highly desirable presently while the histoenzymological and chemical features of the otosclerotic disease are being established step by step.

A histochemical feature which has *not* been studied yet, as far as we know, is the occurrence of sulfhydril groups involved in some of the evolutive stages of the otosclerotic *disease*. *Biochemically the SH* groups are widely spread in proteins, they are essentially constituted by the two sulf

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tiously analysed This may occur by direct coupling in presence of tyrosine and histidine as well as with elastic tissue

Owing to these facts some authors consider as negative results the different shades of pink found after the DDD reaction But for studying our problem instead of any *a priori* opinion it seems more important to compare first the results of the DDD reaction in normal and pathological stapes

Studying six normal platina obtained at necropsy from subjects clinically free of any middle ear disease (ages ranging from 35 to 78 years) we observed the following facts the reaction results constantly in a uniform and very pale yellowish shade evenly distributed on all the bony structures two histological sites displayed a deep pink shade that may be considered as positive These are

1 the cells of the mucosa covering the outer part of the bony structure

2 the endothelium of the small vessels that open their way through these structures

But in no case evidence was obtained of any positively stained material located in the platina bony part itself The above positive results are evidently accounted for by the percentage of SH protein molecules normally present in the endothelium and epithelium cells

The picture is *quite* different when otosclerotic stapes are studied SH positive material may then be found in precise histological aspects and locations both depending mainly upon the stage reached by the disease in the *studied focus*

The results gathered from the study of 27 otosclerotic platina may be summarized as follows *During the first—from the histological point of view* stage of the disease (let it be called the blue mantle stage *for general* agreement s sake) some positive results are observed strictly *limited around* the enlarged pathological cellular lodgings (these cells are probably always chondrocytes) So these SH *group localizations* are roughly superimposed to what has been described as *blue mantles* by Manasse in 1890 To judge by this first stage of the disease we must note that the positive reactions remain as a rule *rather* discrete but one must consider that the masses of tissue in cause here are very small *ones* almost of the cytological scale

The second stage is the one of the extending lytic *areas* and the beginning of the remodelling of the focus that is a mixture of reconstruction fibrillar and osteoid processes *that* are generally mixed in alternating neighbouring foci These are *intricated* processes that last certainly for a long time As a *matter of fact* they define the otospongious stage itself During this stage the DDD reaction is positive in the majority of cases As far as functional implications may be drawn from histological static pictures this positivity is more evident during the destruction stages or lytic ones than during the reconstruction ones these last ones being labelled by the presence of fibroblasts into the focus

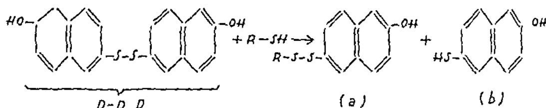
Nevertheless the intrication of these *remodelling* stages of the disease is obvious and one may observe on the same platina *different* stages side by

hydril amino acids cysteine and methionine and by various thiol enzymes (we include glutathione in this last group). A point must be immediately emphasized: the normal collagen is deprived of any SH groups. This is a most important fact owing to the constitution of the normal ossicles and bony capsule of the cochlea that are fibrillar bones particularly rich in collagenous fibers (Faserknochen of the German histologists).

METHODS

It is generally agreed that the most specific technic for studying histochemically the SH groups is the method of Barnett and Seligmann using the substrate 2-2 Dihydroxy 6-6 Dinaphthyl Disulfide (DDD reaction).

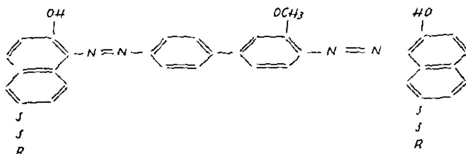
The various steps of this reaction may be summed up as follows:



During the first stage of the reaction the DDD reagent combines with the sulfhydril protein molecule R–SH to form (1) a naphthyl disulfide compound (*a*) which is essential to the reaction and (2) a free naphthyl mercaptan (*b*) that must be eliminated along the following steps.

During these steps washings in an aqueous acetic solution followed by ethyl alcohol and lastly anhydrous ether baths remove the mercaptans and the excess of the DDD reagent absorbed on the tissues. Thus there remains only the (*a*) fraction during the further stages.

The final step leading to the precipitate of an azo insoluble dye *in situ* is effected by treating the slides with a diazonium salt. We used for this purpose both the Fast blue B salt and the Fast black K salt. These salts combine with two naphthyl moieties to give an insoluble azo dye after the following reaction:



When using diazo blue the positive results of the reaction are spread along a colour scale from purple blue to deep pink. The different shades of pink are the expression of a mono coupling of the azo dye and they must be cau-



Fig. 1. Localization of the sulfhydrils reactive groups at various stages of the otosclerotic focus. Enlargement 600 diameters. DDD reaction for sulfhydril groups after Barnett and Seligmann

side the SH positive reactions being found side by side with negative lytic zones and this fact constitutes by itself an important mode of control the possibility of diffusion artefacts being thus excluded

During the last stage that is the real otosclerotic one when the reconstruction of bone is on the way of completion and the ankylosis is being established the DDD reaction becomes always negative and one finds again the same pale yellowish non specific stain evenly distributed over the whole of the bony structure similar then to the one observed on normal platina

To sum up—not considering the many possible cases where such a too clear cut classification may be discussed—we note that the SH groups are *to be found in small amount at the beginning of the disease then they grow* steadily during the otospongious stages and finally disappear quickly when new pathological calcification begins

The following point must be emphasized the positive reaction is never a heavily stained one as these found in the hair roots for instance But the *presence of SH groups in small number can nevertheless be ascertained* for the following reasons and controls

The location of the positive reaction

The positive stained tissue is always well limited around the lytic areas and *we never observed any diffusion of the colour the borders* were always sharply limited

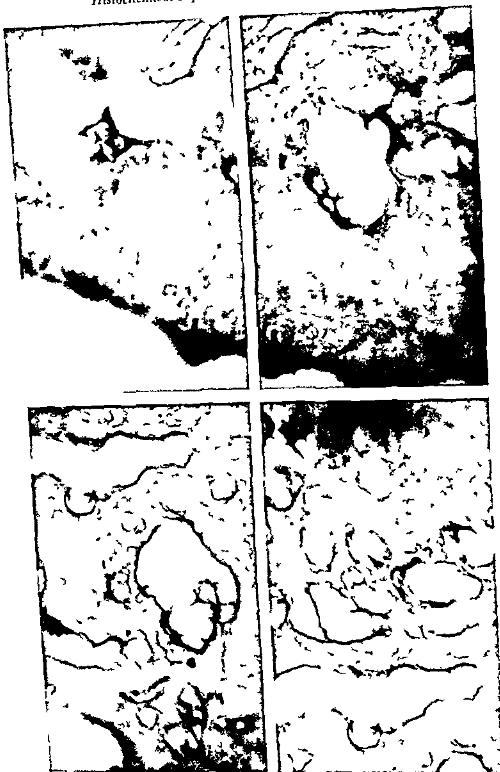
Controls

As for all histochemical studies they are obviously necessary in this case

1 The first control was established by using another reaction for demonstrating the SH groups this was the alkaline tetrazolium reaction proposed by Pearse for SH groups Using neotetrazolium as coupling dye this reaction was done on alternative slides so that we were able to compare exactly *its* results with those of the DDD reaction Both reactions give results of the same value in the same locations

2 All along this study we were impressed by the fact that the localizations of the SH groups were in each case similar and superimposed to those of *the glycoprotein compound which we have shown previously to be* partly formed of glycogene and that constitutes part of the osteoid border zone of each evolutive focus So we verified that a one hour amylase incubation does not at all modify the positive SH response of the reaction

3 Another control must be done to eliminate the following possible artefact a direct azocoupling between tetrazotized diorthoanisidine (diazo blue) and some collagene terminal or residual amino acids we have already insisted on the fact that the otospongious stage is characterized by an important osteolytic activity *This activity involves the very rich collagenous* fibrillar material of the platina bony structures On the other hand it is a well established fact that the DDD reaction may develop a light pink colour at contact with collagenous tissue this owing to the possibility of direct azo



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During the last stage, that is the real "otosclerotic" one, when the reconstruction of bone is on the way of completion and the ankylosis is being established, the DDD reaction becomes always negative and one finds again the same pale yellowish non-specific stain evenly distributed over the whole of the bony structure, similar then to the one observed on normal platina

To sum up—not considering the *many possible cases where such a too* clear cut classification may be discussed—we note that the SH groups are to be found, in small amount, at the *beginning of the disease, then they grow* steadily during the otospongious stages and finally disappear quickly when *new pathological calcification begins*

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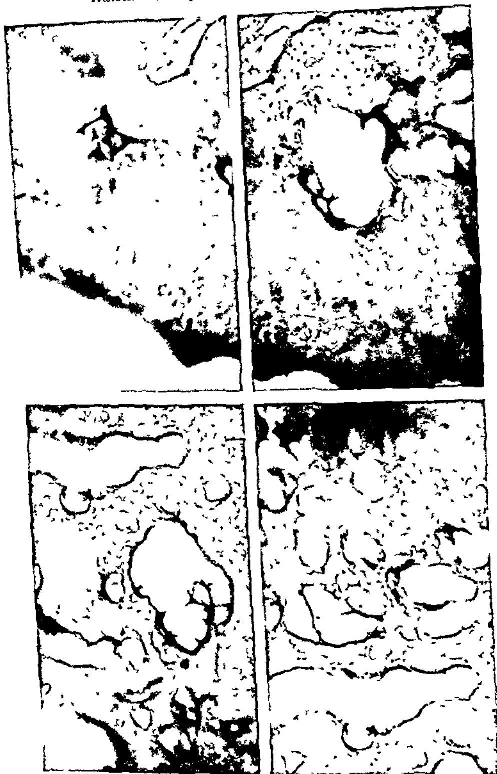


FIG 1 Localizations of the sulfhydrils reactive groups at various stages of the otosclerotic focus (00) diameters DDD reaction for sulfhydril groups after Barnett and *Seligmann*

coupling between diazo blue and tyrosine or (and) histidine residual groups We have tested this possibility on our material by incubating for three minutes slides in a solution of diazo blue at pH 7 4 This resulted in a non specific yellowish stain evenly distributed over the whole tissue The difference with the clear cut light purple locations we obtain when the reaction is positive is so obvious that the possibility of such artefacts can certainly be discarded

4 *The last control is obviously the study of the inhibition of the DDD* reaction

From this point of view the SH groups may be divided into two classes In the first one the SH groups are not tightly bound to the protein molecules and the SH groups are then easily oxydized or reduced in the second one they are on the contrary firmly bound to the protein and it is then much more difficult to alter their reactivity It seems that the SH groups we are dealing with here belong to this second group

We used two types of blocking procedures

1 Carboxyalkylation using halogenates of the acetic acid (iodoacetic acid)

2 Oxydation by acidified iodine solution (pH 3 5) (lugol mixture)

Actually we did not succeed completely in preventing the positivity of the reaction even in using incubation times up to 24 hours We only obtained large attenuations of the colour finally developed This must be correlated to the studies of *Bacq* who biochemically established the fact that the reactivity of protein bound SH functions with monoiodoacetic acid is much slower than with substrates of a lesser molecular weight such as glutathione for instance

DISCUSSION OF THE RESULTS

What are the origin and the meaning of these SH groups within the oto sclerotic focus?

Owing to the lack of any SH groups in collagene tissue the origin of these SH groups is to be found in the ground substance This one is certainly involved in the cleavage of the molecules that defines the lytic activity of the disease during the stages at which SH groups are evidenced Most probably it is not the sulfated mucopolysaccharides that are in cause Biochemically the transformation from SO groups to SH ones would not be easily understood The oxydation reactions being here far more easily affected than reduction ones

But there are *some SH containing substances normally present in the so called bony matrix* Castor for instance has found in osseomucoid 1 13 g of cystine and 1 09 g of methionine for 100 g of dry bony tissue Besides Belanger using cystine and methionine labelled with S^{35} has demonstrated that the amino acids were integrated in the synthesis record of the hyper trophic cells of the cartilage A very active integration was also found in the formative zones of the bone where the osteoblasts are involved in the proce

dure and after two days time extracellular activity would appear in the cartilage matrix of the hypertrophic zone

In spite of the fact that such experiments using labelled complex molecules do not provide evidence that these molecules remain as such when they are incorporated into the calcifiated matrix of cartilage it is highly probable that their SH groups remain chemically available because they do not enter into classical peptide links and even if they provide disulfur links it is probable that under lytic pathological processes these disulfur bridges are easily altered to sulfhydril ones It is even quite possible that the degradation products so available are used again during the remodelling pathological processes *in situ* to build up new bone From this point of view we have demonstrated the existence of transglycosylases in otosclerotic focus during these same stages and these branching enzymes though limited in their action to the glyco moieties of the glycoproteins molecule may well be coupled with proteases whose synthetic power is a well known fact

This brings us to consider the problem of the SH depending enzymes Among the many thiol enzymes the most important here seems to us the osseous proteases these proteolytic enzymes belong to the class of the cat hepsins (or catheptases) studied by Willstatter and Bamann They are characterized mainly by their optimum pH activity that is situated between pH 4 and 7 The activity of these catheptases is dependent on the existence of SH groups in their proteic molecules they are activated by some SH containing substance cysteine and glutathione for instance and the trans formation from SH to SS bonds by oxydation inactivate completely the enzymatic activity

P Carlier has studied the proteolytic enzymes of the bone using the long bone diaphysis of the rabbit The enzymatic activity seems to be directly correlated to the importance of cellular involvement—but even if the *medulla* is thoroughly eliminated there remains a measurable activity in the bony shaft This one is considerably enhanced by cysteine glutathione and by ascorbic acid That is an interesting fact as we have demonstrated the exi stence *of this C* vitamin in the otospongious focus when new fibroblasts appear growing The pathological stage—the otospongious one—during which the SH groups are mainly found is *defined by* the limited osteolytic process It seems quite reasonable to consider that the SH groups so evidenced may at least partly belong to the active proteolytic enzymes which are part of the very complex *enzymatic picture* of the disease The interest of the SH groups whatever their origins may be—and it well may be double one—is that they can be considered as a good index of this osteolytic activity and offer a mean of diagnosis *not only* of the disease but of its stage too

RÉSUMÉ

La mise en évidence de groupements sulfhydrilés au niveau de foyers otospongieux au cours des premiers stades de leur évolution *nous paraît* revetir un double intéret

Ils indiquent une activité protéolytique au niveau de la substance fondamentale de l'os et constituent, également, un trait caractéristique, sur le plan histochimique, des premiers stades de l'affection

ZUSAMMENFASSUNG

Die Demonstration von Sulfhydrilgruppen im Bereich der otosklerotischen Erkrankung im ersten Stadium ihrer Entwicklung scheint von besonderem Interesse Eine proteolytische Aktivität in der Knochengrundstubstanz ist hiermit angezeigt, was auf dem Gebiete der Histochimie charakteristisch fur die ersten Stadien der Erkrankung ist

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QUANTITATIVE ENZYMATIC CHANGES IN NEURONS AND GLIA OF THE LATERAL VESTIBULAR NUCLEUS DURING CENTRAL COMPENSATION AFTER UNILATERAL VESTIBULAR NEUROTOMY

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The vestibular nerve was sectioned in porus acusticus internus on the right side in two groups of rabbits When central compensation was attained one group was subjected to rotational stimulation for 25 min per day for 7 days All animals were killed two weeks after operation

Succinoxidase activity was measured on isolated Deiter s giant nerve cells and glial cells in the lateral vestibular nucleus Zeuthen s micro diver technique was used for the activity determinations In the operated group succinoxidase activity was increased 100 % in both neurons and glia of the affected side while the control side was unchanged In the operated and stimulated group there was an activity increase only in the glial cells of the operated side

INTRODUCTION

It has long been known—from clinical studies and animal experiments—that after destruction of the labyrinth or vestibular neurotomy nystagmus is evoked toward the intact labyrinth Fairly soon the nystagmus disappears as a result of an effect called vestibular compensation The vestibular nuclei are known to be the centers primarily affected by the loss of labyrinthine impulses

Neuroanatomical connections of the vestibular nuclei have been mapped in detail and they are concerning the lateral nucleus better known than those of the other nuclei of the complex Walberg Bowsher & Brodal (1958) showed that primary vestibular fibers have synaptic contact with all the four vestibular nuclei The lateral nucleus is however, only supplied with these fibers in the rostroventral part The fibers terminate on the small and middle sized nerve cells of the nucleus Deiter s giant nerve cells are devoid of degenerating synaptic terminals after vestibular nerve transection The efferents of all neurons in the lateral nucleus run in the vestibulospinal tracts and send collaterals to the reticular formation (Scheibel & Scheibel 1958) The nucleus receives in addition to the primary vestibular fibers afferents from the spinal cord (Pompeiano & Walberg 1957) the cerebellum (Jansen & Brodal 1940) the reticular formation (Lorente de No 1933 Scheibel & Scheibel 1958) and possibly from the contralateral nucleus

Neurophysiological studies have shown changes in impulse recordings in

the nuclei and in adjacent structures when the normal balance between the two labyrinths is broken.

As a response to rotational stimulation of the animal Hydén & Pigon (1960) found a pronounced increase in succinoxidase activity of Deiter's giant nerve cells in addition to a slightly lowered activity in the surrounding glial cells. The neuron glia unit in question demonstrated a number of similarly inverse biochemical reactions at the cellular level during increased functional demands (Hamberger & Hydén 1963).

We have investigated this problem from another aspect trying to evaluate the time factor in the events of the vestibular nuclei during the first weeks after the balance is changed. For this purpose we have followed a respiratory enzyme (succinoxidase) activity with a quantitative cytochemical method. The Deiter's giant nerve cells in the lateral vestibular nucleus of the rabbit were selected. In addition we have measured the enzyme activity in the glial cells in order to explore their possible role in the compensation process concerned.

MATERIAL AND METHODS

Right side vestibular neurotomy and subsequent enzymatic analysis was performed on 19 white rabbits weighing 1.5–1.8 kg. Of the operated animals a first series was analyzed after on the average 16 days. A second series about ten days after operation was subjected to rotational stimulation for seven days and analyzed on the last day of stimulation.

Vestibular neurotomy. The animals were anesthetized by an intravenous injection of Nembutal 0.4 ml/kg. The skull was exposed from a midline incision in the occipital region. The bone was drilled away in a small area above the atlantooccipital membrane. The exposed dura was incised and moved laterally exposing the medulla. After suction of excess of liquor the medulla was carefully moved to the left with a specially made spatula. In this way the nerves in the porus acusticus internus dx were exposed. A micro hook was put around the vestibular portion which was divided.

Preoperative nystagmus of the destruction type immediately ensued. Postoperatively the animals showed symptoms of disturbed vestibular balance i.e. nystagmus against the left side, torsion of head to the right and a tendency for rotation to the right. In 1–3 days the nystagmus and the tendency toward rotation subsided, the right torsion of the head being permanent.

Reactions and food intake were frequently checked and at the time of sacrifice the weight of the animals was generally found to have increased since the day of operation.

Rotational stimulation. The stimulation was induced according to Hydén & Pigon (1960) i.e. by rotating the animals back and forth through 120° horizontally and 30° vertically with 30 turns per minute for 25 minutes each

day for seven days The animals were placed in a tight fitting box with the head away from the center The acceleration and deceleration were comparatively slow and were shown not to cause any damage on the vestibular apparatus (Hyden & Pigon, 1960) In this way symmetrical stimulation of the animal was achieved

Determination of enzyme activity The microdissection technique of Hyden (Hydén & Pigon 1960) was used and the oxygen consumption was measured with Zeuthen s microdiver technique (Zeuthen 1953)

The animals were killed by an air embolus and the brain removed immediately Slices from the medulla oblongata were cut through the lateral vestibular nucleus The Deiter s giant nerve cells were dissected out freehand together with the surrounding glial cells which were subsequently separated from the neurons by gentle manipulation with the dissecting instrument in a drop of incubation medium Each nerve cell and glial clump which was of the same volume and dry weight as the corresponding neuron (Hyden 1959) were introduced into separate microdivers along with a small volume of succinoxidase incubation medium In this way one nerve cell and one glial clump from the right and left sides were analyzed during each diver experiment

Oxygen consumption was determined manometrically for 2 3 hours and was expressed as 10^{-4} μl O_2 per sample per hour

Incubation medium Na_2HPO_4 KH_2PO_4 buffer pH 7 4 37 5 mM cytochrome c 8 6 $\times 10^{-2}$ mM Na succinate 25 mM $AlCl_3$ 0 5 mM (Slater 1949 Potter, 1957 Hyden & Pigon 1960)

RESULTS

Control values of succinoxidase activity in Deiter s giant nerve cells and in the surrounding clump of glial cells are 2 2 and 4 2 $\times 10^{-4}$ μl O_2 per hour respectively as shown by Hyden & Pigon (1960)

Control experiments (four animals) where the operation was performed in all parts except the final nerve transection gave bilaterally equal results, 3 8 for neurons and 4 2 for glia These values are taken as zero day values, in Fig 1 in order to establish the activity changes resulting from the nerve transection per se

Neurotomy The results of succinoxidase determinations on right (neurotomy) and left sides in the compensated animals are listed in Table 1 The neurons and glial cells show a 100 % increase in enzyme activity on the operated side On the left side both components showed virtually no change in activity

Neurotomy + rotational stimulation 7 × 25 min rotational stimulation started on the ninth day after operation The activity was as shown in Table 2

TABLE 1 *Effect of vestibular neurotomy on succinoxidase activity in Deiter's giant nerve cells and glial samples*

Mean time after neurotomy 15 days
Expressed as 10^{-4} μl O_2/hr

	Nerve cell	p^x	Glia	p^x
Right side (neurotomy)	7.9±1.8	0.05	8.7±1.4	0.01
Left side (control)	4.0±0.7		4.9±0.8	

$^x p$ the probability value for a significant difference between left and right side values

TABLE 2 *Effect of rotational stimulation after vestibular neurotomy on succinoxidase activity in Deiter's giant nerve cells and glial samples*

Mean time after neurotomy 16 days
Expressed as 10^{-4} μl O_2/hr

	Nerve cell	Glia
Right side (neurotomy)	3.1±0.5	7.0±1.5
Left side (control)	3.1±0.6	3.7±0.6

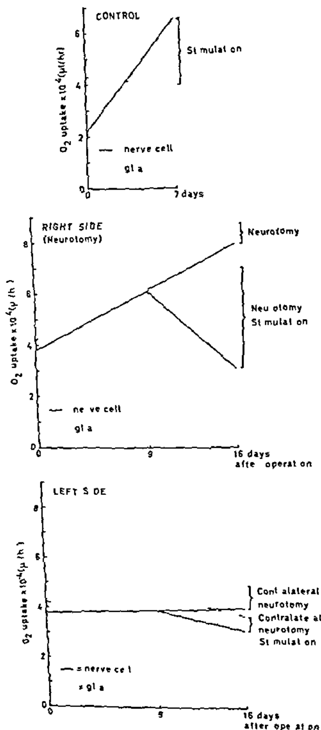
With respect to the nerve cells the succinoxidase activity on both sides decreased to 3.1×10^{-4} μl O_2 per hour indicating a decrease mainly on the neurotomy side. The glial cells also gave a bilateral decrease, small and about equal on both sides.

Microscopic examination of the lateral vestibular nucleus 14 days after unilateral neurotomy did not disclose any pathological changes.

DISCUSSION

In the present study we have found changes—both neuronal and glial—in succinoxidase activity, an important enzyme complex in the oxidative metabolism of the cell. The works of many authors have shown a definite correlation between increased neuronal activity or adequate physiological stimulation and oxygen consumption, glucose consumption, RNA synthesis and other functional parameters as well as structural features (Utina, Nechaeva & Brodskii 1960, Chentsov, Borovyagin & Brodskii 1961, Geiger 1962, McIlwain 1962). Thus by using the succinoxidase activity as indicator of cell function we put forward the question if the findings reflect changes in the biochemical mechanism of nerve and glial cells parallel to existing electrophysiological and clinical observations.

The succinoxidase activity in the control operation experiments shows that the mere manipulation of the brain, inevitably associated with operation, induces an increased activity in the nerve cells while the glial cells



F g 1 Survey of chang s in nerve cells an l glial cells Top figure lrawn after results from Hydén & Pigon (1960)

on the contrary, were unchanged. The results on glia are in accordance with the findings made with qualitative histochemical enzyme determinations (Friede 1962, Rubinstein, Klatzo & Miquel 1962, Mossakowski 1963) while the nerve cell reaction seems to be in contrast to the histochemical data.

Approximately two weeks after right side vestibular neurotomy both the neurons and glial cells on this side had a doubled succinoxidase activity while on the contralateral side practically no change was observed. The response of the nerve cell on the right side is similar to the reaction of the nerve cell after vestibular stimulation on intact animals reported in the work of Hydén & Pigon (1960). However, they observed glial cell changes of opposite direction (Fig. 1). Increased activity and deprivation of the normal stream of impulses apparently cause different neuron-glia metabolic relations.

The present results two weeks after unilateral neurotomy can be explained as a biochemical expression of a higher activity state in the cells of the lateral vestibular nucleus of the affected side.

The immediate changes in impulses to the vestibular nuclei after the nerve transection have been recorded by electrophysiological techniques. Gernandt & Thulin (1952) implanted microelectrodes in the nuclei of both sides. After nerve transection the nuclei on the affected side demonstrated very little or no activity whereas on the other side the spontaneous discharges were unchanged. However, DeVito, Brusa & Arduini (1956) found no striking decrease after vestibular nerve transection and even cerebellectomy had no effect.

Thulin (1960) in presenting a clinical material reviewed the central compensation phenomenon after monolateral labyrinth destruction. He concludes that a new activity state is being built up in the vestibular nuclei on the affected side causing a gradual return to the original state. The eventual origin of the impulses to this reactivation is not precisely known.

The second series of rabbits with transected vestibular nerve was subjected to rotational stimulation. This was done in order to determine whether a "normal" (Control in Fig. 1) reaction would be superimposed on the aforementioned effects of transection. Bilaterally the glial cells reacted in analogy with the results of Hydén & Pigon (1960). The nerve cells of the neurotomy side however did not behave like the nerve cells of intact control animals: *the decrease in activity on the neurotomy side was most conspicuous* although the very slight effect on the intact side was also quite remarkable. The virtually unchanged activity on the left, non-operated side demonstrates that the vestibular system cannot function as two independent halves, at least from a biochemical point of view.

The decrease in succinoxidase activity of the neurons on the neurotomized side after stimulation indicates an inhibition of the mechanism that gave the higher activity state.

Gernandt & Thulin (1952) in making electrophysiological studies on unilaterally labyrinthectomized cats, found no change in the electrical activity

of the vestibular nuclei on the affected side and a normal increase on the intact side after rotational stimulation. On cathodal polarization of a labyrinth De Vito, Brusa & Arduini (1956) obtained augmentation of firing of the neurons in the ipsilateral Deiter's nucleus and a high percentage of blocking in the contralateral nucleus. Cerebellar polarization can also block the spike discharges in Deiter's nucleus.

The reticular formation is evidently a co-ordinator of stimuli to the vestibular nuclei. Unilateral stimulation in the midbrain reticular formation evokes bilateral vestibular responses (Feldman, Wagman & Bender 1961). The activity pattern as measured in the reticular formation is, however, usually opposite to that in the vestibular nuclei during labyrinthine stimulation (Gernandt & Thulin 1952).

Following unilateral labyrinthectomy in patients there is an increased sensitivity to hot water irrigation on the intact side due to a release of facilitatory impulses to the vestibular apparatus from the controlling structures discussed (Fluur 1961). The present enzyme determinations on the intact side indicate an altered response, although the eventual correlation with the clinical findings is at present unexplained.

ACKNOWLEDGMENT

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ZUSAMMENFASSUNG

Bei zwei Gruppen von Kaninen wurde der nervus vestibularis im Bereich des porus acusticus internus auf der rechten Seite abgetrennt. Sobald die zentrale Kompensation erreicht war, unterwarf man eine Gruppe einer rotatorischen Stimulation von 25 Minuten unter 7 Tagen. Die Tiere wurden 2 Wochen nach der Operation getötet.

Die Succinoxidaseaktivität wurde an isolierten Deiters Riesennervenzellen und Gliazellen in dem lateralen Vestibulariskern gemessen. Zeuthens micro-diverteknik wurde benutzt. Innerhalb der operierten Gruppe zeigte sich eine 100 % Steigerung der Succinoxidaseaktivität sowohl für die Nervenzellen als auch für die Gliazellen auf der behandelten Seite, während die Kontrollseite unverändert war. Innerhalb der operierten und stimulierten Gruppe zeigte sich eine Aktivitätssteigerung nur für die Gliazellen auf der operierten Seite.

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RETROGRADE JUGULAROGRAPHY IN DIAGNOSIS OF GLOMUS TUMOURS IN THE JUGULAR REGION

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The anatomy, pathology, clinical features and diagnostic problems of glomus jugulare tumours are described. Twelve histologically verified cases examined with retrograde phlebography of the internal jugular vein are reported. The value of the method is stressed in assessing the extent of the tumours before operation, especially in those cases where the tumours originate from the adventitia of the superior bulb of the vein.

In 1941 Guild reported the normal occurrence of some formerly unknown growths in the region of the temporal bone in man. They were of the size of rice grains and situated chiefly around the superior bulb of the internal jugular vein and along the tympanic branches of the IXth and Xth cranial nerves. Guild proposed the term glomus jugulare for such a growth.

The first report of a primary glomus tumour originating in the glomera of the middle ear was published by Rosenwasser in association with Guild in 1945, since when some two hundred such cases have been reported (Blomqvist et al. 1954, Capps 1957, Gastpar 1961). Ten out of 54 tumours of the middle ear reported by Bradley & Maxwell (1954) were glomus tumours. Following up 47 cases of tumours of the middle ear Figi & Weisman (1954) found that 16 of them diagnosed as haemangioendothelioma were in fact glomus tumours.

With the extension of our knowledge of the pathologic, clinical and radiographic features of these tumours there has been an increase in the number diagnosed. Several radiographic techniques have been used for diagnostic purposes. The value of carotid angiography in diagnosing tumours of the carotid body and glomera jugulare has been increasingly realized. In this paper we shall call attention to the advantage of retrograde jugularography in diagnosing glomus jugulare tumours.

Anatomic and Pathologic Features

In an examination of 88 normal temporal bones (44 subjects) Guild (1953) found 248 glomus formations, about one half of which were situated in the adventitia of the dome of the jugular bulb, one quarter were in the

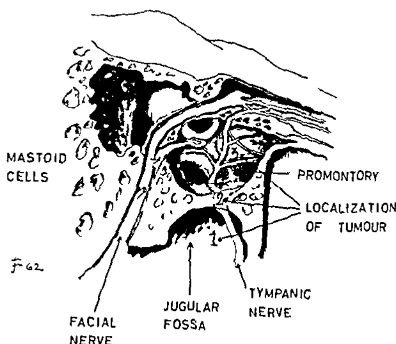


FIG 1 Predilection sites for glomus formations and glomus tumours *1*, The adventitia of the dome of the jugular bulb *2*, along the tympanic nerve, *3*, along the auricular branch of the vagus nerve

mucosa of the cochlear promontory, along the tympanic plexus portion of the tympanic nerve, and another quarter were found along the auricular branch of the vagus, sometimes as far peripherally as the facial canal (Fig 1) *Each ear contained as a rule at least one glomus, and in 68 out* of the 88 temporal bones there were 2 or 3 There was, moreover, a tendency for bilateral similarity The number of glomera proved greatest at middle age, and decreased thereafter The diameter of the glomera varied from 0 1 mm to 1 5, most of them being about 0 5 mm They usually had the form of a flattened ovoid

Like the carotid body, they were composed of epithelioid cells embedded in a capillary network and surrounded by a thin fibrous capsule The ratio of capillaries to epithelial cells usually varied with the latter in the majority Out of 78 glomera, 55 were classed as cellular and 23 as vascular

The glomera jugulare formations even those associated with the auricular branch of the vagus are innervated by the IXth cranial nerve presumably via anastomoses *The blood supply is provided by the ascending pharyngeal* artery by way of its tympanic branch

Similar structures to those in the glomus jugulare were found by Birrell (1955) around the superior vagus ganglion

Tumours originating from glomus formations have a structure that does not differ greatly from the normal Le Compte (1948) divides glomus tumours into three groups

1 Usual type The commonest ones, the histologic picture of which is identical with that of normal glomus tissue
2 Angioma like type
3 Adenoma like type

Tumours of the glomus jugulare are histologically benign but clinically they may display a malignant mode of growth A few cases of true malignancy with remote metastases have been reported however (Rosenwasser, 1958 Shambaugh 1955)

Because of its origin and possible function as receptor the glomus jugulare tumour has also been designated chemodectoma or non chromaffin para ganglioma

Clinical Features and Diagnosis

Tumours of the glomus jugulare grow extremely slowly A long history is highly characteristic, commonly covering 3 to 7 years and sometimes more than 20 Two kinds of symptoms can be distinguished according to the site of origin of the tumour

1 Tumours arising from the superior bulb of the jugular vein and around the jugular foramen chiefly cause neurologic symptoms similar to the jugular syndrome, with symptoms from the cranial nerves IX to XII (Ekstrand & Gejrot 1962)

2 Tumours arising from the middle ear are accompanied by primary symptoms reminiscent of those of chronic otitis with hearing impairment discharge from the ear and polyps in the auditory meatus as the first signs A tumour arising from the middle ear is usually known as a tympanic body tumour (Lundgren 1949)

When the tumours destroy the surrounding tissues a combination of neurologic and aural symptoms is usually experienced

The tumours are usually not discovered until they break through the tympanic membrane or the wall of the auditory meatus and give rise to a polyp which bleeds readily In some cases they may grow towards the orbit or even penetrate the dura of the posterior cranial fossa

The diagnosis of tumour of the glomus jugulare is usually made on the basis of histological examination of a meatus polyp or of histological findings at operation for chronic mastoiditis where easily bleeding granulations have come to light

Radiographic Features

Like the symptoms the radiographic findings in cases of glomus tumours vary according to the situation and extent of the growth As a rule the tumour does not destroy the surrounding bone until quite a late stage Earlier the growth is difficult to distinguish from mastoiditis Sickert (1956) found destruction of bone in only one third of his advanced cases

The radiographic diagnosis of glomus tumours has been dealt with by



FIG. 2. A, normal jugularogram. Anterior-posterior view. Both jugular veins and transverse sinuses are opacified. B, normal jugularogram. Lateral view. Note the filling of the inf. petrosal sinus.

Riemenschneider *et al.* (1953), Guillen & Portmann (1959) and Hawkins (1961). According to Hawkins (1961) the first radiographic sign of glomus tympanicum is a clouding of the mastoid cells. If, as is often the case, there is inflammation, there is also destruction of the antrum and the region of the tympanic cavity.

If the tumour arises from the superior bulb, destruction of bone can be seen around the jugular foramen. Secondary features are enlargement of the mastoid foramen, the grooves for the mastoid emissary veins and the foramen for the vertebral artery in the transverse process of atlas.

A few cases have been diagnosed by means of carotid or vertebral angiography (Riemenschneider *et al.* 1953, Hooper 1955). Since glomera are supplied by the tympanic branch of the ascending pharyngeal artery, that is to say the terminal branches of the external carotid artery, the contrast medium must be injected into the external or possibly the common carotid artery. Only large tumours can be supplied via the vertebral artery.

Intracranial glomus tumours have been demonstrated by encephalography (Hierons 1954).

Since 1959 retrograde jugularography, that is venography of the internal jugular vein, has been used at this hospital for studying the venous flow from the brain in planned dissection of the neck (Gejrot & Lindbom 1960, Gejrot & Laurén 1961). The technique used, utilizing the Seldinger guide wire instruments, has been described in detail by us in these papers.

The tip of the catheter is placed in or just below the superior jugular bulb. Twenty milliliters of 45 per cent urografin is injected with the highest possible manual pressure; two or three films are then exposed while the vein is compressed distally. Two routine projections are used, namely, the usual occipital projection angled 30° in the caudal direction, and a lateral projection, slightly oblique to avoid over projection from the other side.



Fig 3 Case 1 Constricted segment of internal jugular vein with poor opacification

Both jugular veins together with the sigmoid and lateral sinuses are usually contrast filled The normal findings are illustrated in Fig 2

Retrograde jugularography with the aid of catheter was first reported by Nick *et al* in 1955 in a case of neurinoma of the hypoglossal nerve Later Petit Dutaillis *et al* (1958) used the method in a case of two glomus tumours blocking the vein in the right jugular foramen

The following 12 cases of glomus jugular tumours were examined by this method 11 of them at this hospital one at the Central Hospital Jonkoping and one at the City Hospital of Norrkoping

Reports of Cases

Case 1 A man aged 61 years who underwent a radical mastoidectomy in 1938 for chronic infection of the right mastoid Histological examination revealed haemangioma like granulations Further operations were performed in 1947 1955 and 1959 for easily bleeding polyps On the histological findings in 1959 glomus tumour was diagnosed A radiographic examination in 1961 including tomography of the region around the jugular foramen revealed no abnormal conditions

Retrograde jugularography of the right internal jugular vein in 1961 indicated an obstruction just below the base of the skull (Fig 3) In angiography of the right

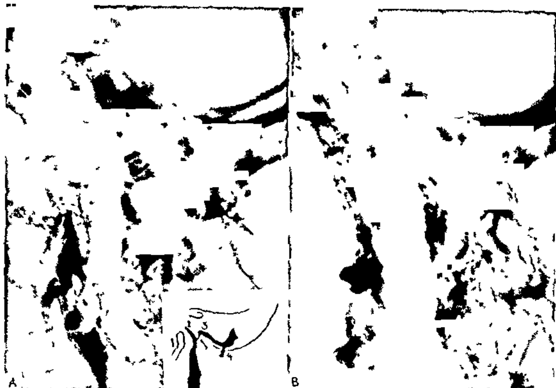


Fig. 1. Case 2. A, constriction of jugular bulb (*arrow*) (*1*, head of mandible, *2*, inferior petrous sinus, *3*, dome of jugular bulb, *4*, mastoid emissary vein). *B*, normal side (unusually wide).

internal carotid artery, the left sigmoid sinus and the internal jugular vein were *opacified*. Only the right transverse sinus and a stump of the right sigmoid sinus a few centimeters long were visualized.

Case 2. A man aged 46, who received treatment in 1956 for left sided otitis. Subsequent hearing loss was ascribed to adhesive otitis, and myringotomy and politzerization were performed. In 1956 there was paralysis of the abducens nerve the cause of which was not revealed by neurological examination. An exploratory tympanotomy in 1960 revealed a pea sized dark growth above the round window and promontory; it did not bleed easily. Histological examination disclosed a glomus tumour. There was no postoperative improvement of the hearing. At reoperation only adhesions were found. Carotid angiography and pneumo- and encephalography performed in 1956 gave no information.

Radiography of the ear in 1960 revealed a diffuse clouding of the mastoid cells, but no definite evidence of bone destruction. Nor did tomography of the jugular foramen bring to light such destruction (right side larger than the left).

On retrograde jugularography of the left internal jugular vein in 1960 there was practically complete constriction of the passage through the jugular foramen (Fig. 1). Right sided retrograde jugularography showed that the whole of the upper part of the right internal jugular vein with the bulb and the caudal part of the sigmoid sinus were considerably wider than on the left side. (This is consistent with the radiographic findings with the respect to the jugular foramen.)

Case 3. A woman aged 51 years with left sided paralysis of the recurrent laryngeal nerve for the previous 5 years (since 1957). Recently, there had been an impairment of the sense of taste, and the *signe rideau* phenomenon. Encephalography and



Fig. 5. Case 3. Pedicled *polypoid* tumour extending downwards in the internal jugular vein (arrows).

vertebral angiography in 1958 showed *no signs of* a tumour. In 1961 there was hearing loss and dullness in the left ear. *Myringotomy* of a reddish membrane caused copious bleeding. Radiographs revealed *destruction* of the occipital border of the *left* jugular foramen. On admission *to the* Karolinska Hospital in 1961 the patient had paralysis of the recurrent laryngeal nerve, atrophy of the tongue, the *signe rideau* phenomenon, slight *facial* paralysis and atrophy of the sternocleido*mastoid* and trapezius muscles on *the left* side. Radiograph*ical* examination of the ear and *base of* the skull showed that the left *jugular foramen* was considerably larger than the right and that there was no distinct border. On the *left side* the mastoid cells were *clouded*.

Retrograde jugularography of the *left* internal jugular vein in 1961 showed it to be completely obliterated at the *jugular* foramen. The vein contained a filling defect, which extended about 1 cm below *the* base of the skull. Dorsal *to this* there was a narrow lumen which extended upwards to about one centimeter *below* the base of the skull. The left *sigmoid* sinus was opacified *through the* collateral venous network *in the region*, probably through the mastoid *emissary* vein (Fig. 5). At



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Retrograde jugularography of the left internal jugular vein in 1961 showed it to be completely obliterated at the jugular foramen. The vein contained a filling defect, which extended about 4 cm below the base of the skull. Dorsal to this there was a narrow lumen which extended upwards to about one centimeter below the base of the skull. The left sigmoid sinus was opacified through the collateral venous network in the region, probably through the mastoid emissary vein (Fig. 5). At



Fig. 6. Case 4. A, normal side (1, mastoid emissary vein, 2, condylar emissary vein, 3, inferior petrous sinus). B, convex, total occlusion of the internal jugular vein just below the jugular foramen (arrow).

operation the sigmoid sinus and jugular vein was opened and the tumour extirpated. Histological examination showed a glomus tumour.

Case 4. A woman aged 65 years, who had been suffering from aching and slight facial paralysis on the right side for 8 years (since 1953). On myringotomy in 1954 a blood-stained fluid escaped. In 1960 the facial paralysis became total. Polyp like growths in the auditory meatus were removed in 1960–62. Histological findings inflammatory polyp. On admission to the Karolinska Hospital there was total facial paralysis of the peripheral type, reduced sense of taste and impaired corneal reflex on the right side. Radiographical examination of the ear showed that the right mastoid cells were clouded with thickening of the mucous membranes. There was no evidence of destruction. Right sided angiography of the internal carotid artery [sic] showed that the venous flow was through the left internal jugular vein. No branches to the tumour region were found. On the right side the transverse sinus was opacified to the level of the sinus—dura angle, although no tumour like border was evident.

Right sided retrograde jugularography suggested total obstruction at the base of the skull. On retrograde injection into the left internal jugular vein the right sigmoid sinus was opacified, but not down into the vein (Fig. 6).

Case 5. A woman of 62 years, who had been receiving treatment for 11 years (since 1951) for right-sided hearing loss and tinnitus. In 1951 the tympanic membrane was bluish-red and a glomus tumour was suspected. Radiography of the ear revealed clouding of the mastoid cells. In 1954 right-sided mastoidectomy was performed, at which an easily bleeding tumorous mass was found in the antrum and middle ear. Histological examination showed glomus tumour (adenoma-like type). In 1957 there were headache, dizziness and right facial paralysis. Inspection disclosed a pale red nodular infiltration of the upper part of the middle ear, which was ascribed to a local recurrence, and radiation therapy was performed. Apart from tinnitus there



Fig 7 Case 5 Convex slightly lobular obstruction of internal jugular vein (arrow) A antero posterior view (1 orbit 2 head of mandible 3 retromandibular vein) B lateral view

had been no symptoms since 1959 At a follow up in 1962 the neurological status was normal apart from mild facial paralysis In 1962 right sided retrograde jugularography was performed The catheter could not be introduced more than about 6 or 7 cm above the puncture site (normal 10–13) In the upper part of the vein there was total obstruction convex downwards The temporal vein was filled via the retromandibular vein high up on the skull cap, where several small emissary veins were visualized (Fig 7)

Case 6 A man aged 53 years, who, after otitis media 10 years previously, was becoming increasingly deaf in the right ear there were no other symptoms. In connection with discharge from the ear in October, 1960 a polyp like formation was found in the meatus Radiography of the ear showed destruction of the attic, and a simple mastoid operation revealed granulations in the antrum which displayed little bleeding Biopsy specimens showed a glomus tumour On admission to the Karolinska Hospital a pea sized reddish polypous growth was seen in the meatus The neurological status was normal with no nystagmus Radiographic examination of the skull showed the jugular foramen to be larger on the healthy left side than on the right Angiography of the external carotid artery was negative Retrograde



Fig. 8. Case 9. Big, rounded filling defect, expanding the upper part of the int. jugular vein.

jugularography revealed a free passage of normal width through the jugular vein and sigmoid sinus.

Case 7. A woman of 51 years, who, since the spring of 1962, had been receiving treatment for secretory disease of the right middle ear, but without success. Myringotomy resulted in copious bleeding. Explorative mastoidectomy performed on October 15, 1962, revealed extremely easily bleeding tumour tissue. Specimens were taken and a sclerosing medium injected. After the operation there was complete facial paralysis. On admission to the Karolinska Hospital 10 days later there was practically total hearing loss in the right ear. There was no nystagmus and apart from the paralysis the neurologic status was normal. Encephalography of the common carotid artery and retrograde jugularography of the right internal jugular vein showed no abnormal features. Queckenstedt's sign revealed no difference on the two sides on compression of the jugular veins. On November 29, 1962, the sigmoid sinus and superior bulb were exposed after removing the mastoid cells and ligating the jugular vein and external carotid artery below. Tumour tissue was found in the bone above the bulb and beneath the facial nerve in the hypotympanum. The sinus



FIG 9 Case 10 Rounded filling defect in the upper part of the int jugular vein

and bulb were not involved Histological examination disclosed a glomus tumour and a small cholesteatoma like sac covered with squamous epithelium

Case 8 A woman of 65 years who had had bilateral neurogenic hearing loss for 30 years She had been wearing a *hearing* aid for the last 40 years Since the age of 3 years she had had pulsating *tinnitus in* the left ear In 1962 the tympanic *membrane* was found to be severely *inflamed* and vascularized and there was reduced mobility A glomus tumour was suspected and exploratory tympanotomy was performed A typical glomus tissue was found *adherent to the* ...

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Fig. 10. Case 11. Rounded filling defect in the upper part of the int. jugular vein. Lateral view.

at the site of the tumour. Retrograde jugularography showed normal findings. At operation on December 4, 1962, the tumour filling the antrum and middle ear was removed. On ligating the external carotid artery the tinnitus disappeared momentarily. The post operative course was not remarkable except for reduced function of the facial nerve.

Case 9. A woman, aged 67, who received operative treatment for glomus tumour 1953, 1958 and 1962. By control 1963 she had a dry and clean cavity. She had no symptoms from the cranial nerves, beside total loss of hearing of her left ear. Tomography of the jugular foramen revealed expansion of the left foramen without erosion. On retrograde jugularography of the left internal jugular vein a filling defect was seen about 4 cm below the base of the skull (Fig. 8). At operation the vein was opened and the tumour thrombus extirpated.

Case 10. A man aged 21 years, who since March 1963 had been suffering from hearing impairment and tinnitus of the left ear. On admission to hospital a polyp like formation was seen in the meatus. The neurological status was normal. Tomo-



Fig. 11. Case 12. Blocking of the int. jugular vein at the entrance into the jugular foramen. Lateral view left, oblique view right. (Filling of the inf. petrosal sinus in the lat. view.)

graphy of the jugular foramen showed a suspicious destruction of the foramen. On retrograde jugularography via the brachial vein a filling defect was seen in the superior bulb about 2 cm in size and occluding the vein (Fig. 9). At operation the whole tumour which reached the sigmoid sinus was extirpated. The histological examination showed a typical glomus tumour.

Case 11. A woman aged 66 years with tinnitus and deafness of her left ear since 1958. Since 1962 atrophy of the left side of the tongue. On admission to hospital the lower part of the left tympanic membrane was sharp red. Neurological status showed a suspicious paralysis of platysma on the left side and of the left hypoglossal nerve. Angiography of both vertebral arteries and encephalography was normal. Angiography of the left external carotid artery showed a widened ascending pharyngeal artery, pathological vessels on the place of the tumour and a shunting to the internal jugular vein.

Tomography of the jugular foramen revealed an expansion of the left foramen. Retrograde jugularography of the left internal jugular vein revealed a filling defect of the superior bulb about 2 cm below the base of the skull (Fig. 10). The defect seemed to be concentrated to the bulb; a distinct superior border could not be seen. At operation a cherry large tumour could be extirpated from the bulb. The hypotympanic cavity was filled of easy bleeding granulations. The histological examination confirmed the diagnosis of glomus tumour.

Case 12. A woman aged 73, who 1959 was operated for a chronical left sided mastoiditis. In 1963 she had discharge from the ear and a reddish polypous growth in the lower part of the meatus. Biopsy showed evidence of a glomus tumour. Neurological examination showed a slight paralysis of the abducent nerve. Radiography of the skull revealed equal jugular foramina. Angiography of the left common carotid



Fig 10 Case 11 Rounded filling defect in the upper part of the int jugular vein Lateral view

at the site of the tumour Retrograde jugularography showed normal findings At operation on December 4, 1962, the tumour filling the antrum and middle ear was removed On ligating the external carotid artery the tinnitus disappeared momentarily The post-operative course was not remarkable except for reduced function of the facial nerve

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Case 11 A woman aged 66 years with tinnitus and deafness of her left ear since 1958 Since 1962 atrophy of the left side of the tongue On admission to hospital the lower part of the left tympanic membrane was sharp red Neurological status showed a suspicious paralysis of platysma on the left side and of the left hypoglossal nerve Angiography of both vertebral arteries and encephalography was normal Angiography of the left external carotid artery showed a widened ascending pharyngeal artery, pathological vessels on the place of the tumour and a shunting to the internal jugular vein

Tomography of the jugular foramen revealed an expansion of the left foramen Retrograde jugularography of the left internal jugular vein revealed a filling defect of the superior bulb about 2 cm below the base of the skull (Fig 10) The defect seemed to be concentrated to the bulb a distinct superior border could not be seen At operation a cherry large tumour could be extirpated from the bulb The hypotympanic cavity was filled of easy bleeding granulations The histological examination confirmed the diagnosis of glomus tumour

Case 12 A woman aged 73 who 1959 was operated for a chronical left sided mastoiditis In 1963 she had discharge from the ear and a reddish polypous growth in the lower part of the meatus Biopsy showed evidence of a glomus tumour Neurological examination showed a slight paralysis of the abducent nerve Radiography of the skull revealed equal jugular foramina Angiography of the left common carotid



Fig 10 Case 11 Rounded filling defect in the upper part of the int jugular vein Lateral view

at the site of the tumour Retrograde jugularography showed normal findings At operation on December 1, 1962, the tumour filling the antrum and middle ear was removed On ligating the external carotid artery the tinnitus disappeared momentarily The post operative course was not remarkable except for reduced function of the facial nerve

Case 9 A woman aged 67 who received operative treatment for glomus tumour 1953, 1958 and 1962 By control 1963 she had a dry and clean cavity She had no symptoms from the cranial nerves beside total loss of hearing of her left ear Tomography of the jugular foramen revealed expansion of the left foramen without erosion On retrograde jugularography of the left internal jugular vein a filling defect was seen about 1 cm below the base of the skull (Fig 8) At operation the vein was opened and the tumour thrombus extirpated

Case 10 A man aged 21 years who since March 1963 had been suffering from hearing impairment and tinnitus of the left ear On admission to hospital a polyp like formation was seen in the meatus The neurological status was normal Tomo

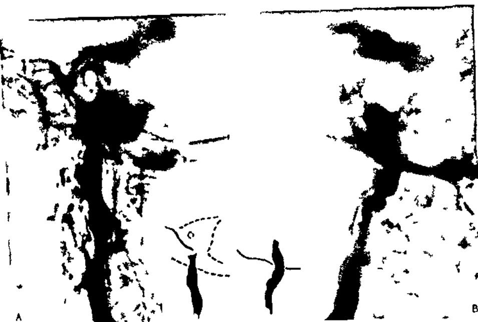


Fig 11 Case 12 Blocking of the int jugular vein at the entrance into the jugular foramen Lateral view left oblique view right (Filling of the inf petrosal sinus in the lat view)

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TABLE 1 *Analysis of cases*

Case	Age	Sex	Side of tumour	Approximate length of history (years)	Operations before retrograde jugularography	Radiography of ear	Radiography of jug foramen	Involvement of cranial nerves	Angiography	R– ju
1	61	♂	Right	20	Radical mastoid op right 1938/ 1942/1955/1959	Clouding	Right = left	—	Int carotid a negative	Po
2	46	♂	Left	4	Tympanotomy	Clouding	Expansion right	XI	Com carotid a negative	Po
3	54	♀	Left	4	—	Clouding	Erosion left	VII IX X XI XII	Vertebral a negative	Pos
4	65	♀	Right	9	Radical mastoid op	Clouding	Right = left	VII	Int carotid a negative	Po
5	62	♀	Right	2	Radical mastoid op	Clouding	Right = left	VII	Int carotid a negative	P
6	53	♂	Right	10	Simple mastoid op	Erosion	Expansion left	—	Ext carotid a negative	Ne
7	51	♀	Right	1	Simple mastoid op	Normal	Right = left	—	Com carotid a negative	N
8	65	♀	Left	3	Tympanotomy	Normal	Right = left	—	Com carotid a positive	Ne
9	67	♀	Left	10	Radical mastoid op left 1953/ 1958/1962	—	Expansion left	—	—	Pos
10	21	♂	Left	½	—	Normal	Susp erosion left	—	—	Pos
11	66	♀	Left	5	—	Normal	Expansion left	VII X	Vertebral a neg ext carotid pos	Pos
12	73	♀	Left	1	Radical mastoid op 1959	Clouding	Right [illegible] left	XI	Ext carotid a pos int carotid a pos	Po

artery showed a shunting between the external carotid artery and the internal jugular vein On the right side the contrast medium filled the jugular vein On the left side the contrast medium was arrested at the sigmoid sinus

Retrograde jugularography revealed a distinct obstruction in the superior bulb (Fig 11) At operation the hypotympanic cavity was filled of tumour growth pressing on the superior bulb and invading the vein The histological examination revealed a glomus tumour

COMMENT

It is evident from Guild's studies that glomus formations usually occur multiply in the ear There is a tendency for them to be located around the jugular bulb (50 per cent of Guild's cases) and otherwise around the tympanic

branches of the glossopharyngeal and vagus nerves Extirpation of a tumour in the middle ear or mastoidectomy in the case of a tumour around the antrum thus does not exclude the possibility of another tumour near the jugular bulb This point assumes importance in deciding the treatment to be given in such cases In case 2 the pea sized glomus tumour at the promontory was probably accompanied by at least one other In three of the cases in which jugularography showed a defect in the bulb of the jugular vein there were neurological symptoms On surgical exposure of the bulb at operation the positive phlebographic findings in the cases 3 9 10 11 12 and the negative one in case 8 were confirmed One patient died during her stay in hospital before phlebography from pulmonary embolism At autopsy a tumour of rice grain size was found in the bulb and there were granulations around the tympanic membrane Post mortem contrast filling through the transverse sinus of the same side showed a small filling defect corresponding to the tumour probably too small to be seen at jugularography *in vivo*

Angiography was performed in ten cases via the external carotid artery the common carotid artery and internal carotid artery In two cases angiography was performed via the vertebral artery In four cases in which the contrast medium was injected into the common carotid artery the findings were positive As has been mentioned earlier opacification of the vessels of the tumour can be expected only if the injection has been made into the external carotid artery or possibly the common carotid Only glomus tumours situated within the cranium can be visualized by angiography of the vertebral artery

The vascular type of Le Compte s three classes of glomus tumour may be expected to be opacified in angiography This type of glomus body comprised about one third of Guild s series

Destruction of the jugular foramen was noted in only one case and here a fully developed jugular foramen syndrome was found In two cases the foramen was wider on the uninvolved side

CONCLUSIONS

The findings obtained by venography of the internal jugular vein with special reference to the *superior bulb* has shown that more attention than hitherto should be devoted to the fact that the most important predilection site for glomus tumours is around the jugular bulb The experience provided by the present series corresponds closely with Guild s in that one half of the glomus tumours originated from the bulb Mastoidectomy is not always the most effective treatment exposure of the bulb and post operative irradiation therapy should always be considered Retrograde jugularography is of great value in assessing the extent of the tumour especially in the cases in which it arises from the adventitia of the bulb and can grow downwards in the vein before involving either the bone wall of the middle ear or the part of the skull base adjacent to the jugular foramen

ZUSAMMENFASSUNG

Die Anatomie, Pathologie und klinische Diagnose der Glomus jugulare Tumoren sind beschrieben Zwolf histologisch verifizierte Tumoren sind mit einer speziellen Phlebographie, retrograder Jugularographie, untersucht Diese Methode hat eine besondere Nutzlichkeit, wenn der Glomustumor seinen Ausgang in der Kuppel des Bulbus jugulare hat

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The damage of the organ of Corti because of noise is well known Prevention of noise injuries has therefore been concentrated chiefly on this aspect It is less known whether noise has other effects on the human organism According to Lehmann (1955 and 1959) a contraction of pre capillary vessels usually follows exposure to noise This vascular response leads to a decrease of the pulse volume and to paleness of the skin and mucous membranes The pulse rate and blood pressure on the whole remained unchanged although a slight rise of the diastolic pressure could be traced However marked changes of the stroke volume were found to take place A noise of 90 decibels could cause the resistance of the peripheral vessels to be doubled and the cardiac output and the stroke volume to be halved (1955) Using the same stimulus exactly the opposite reaction and doubling of the stroke volume was also demonstrated The different types of reaction were considered to be caused by the initial state of the vegetative nervous system The occurrence of the vascular reactions depended on the intensity of the noise When the noise exceeds 90 decibels these reactions can be demonstrated in over 90 % of the individuals tested The reactions could not be related to whether the noise was found to be unpleasant or not and psychological factors were therefore considered to be without importance The reaction persisted as long as the noise lasted and pre reaction conditions returned soon after cessation of the noise Jansen (1961) has examined the influence of sounds of 95 decibels intensity but otherwise of different qualities He found that the vascular reactions were effectively released by white noise This is important since industrial noise has a broad spectrum and is thus comparable to white noise Jansen 1961 investigated workers who had worked in noisy conditions for many years and who stated that they did not find it unpleasant He found the usual vascular reactions in these subjects and concluded that adaptation does not occur

The reactions described by Lehmann and Jansen are very interesting The results obtained by these authors we think must be due to an increased sympathicotonus which in turn ought to lead to functional changes in every organ innervated by the autonomic nervous system

The object of the present investigation has been to determine whether a loud noise over a limited period of time has any effect on the cardiac output and the pulmonary artery pressure

MATERIAL AND METHOD

Ten patients were examined Some relevant data are shown in Table 1 None of them had been troubled by poor hearing Eight of the ten patients were examined audiometrically Seven of them had normal hearing in one or both ears except for a few slight high tone losses One patient had a slight loss of hearing indicating senile degeneration of the auditory nerve with normal hearing at low tones up to 1000 cps in the best ear Continuous

THE INFLUENCE OF NOISE ON SOME CIRCULATORY FUNCTIONS

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Using cardiac catheterization we have investigated oxygen uptake, arterio venous oxygen difference, cardiac output, cardiac rate, cardiac stroke volume and the pressure in the pulmonary artery in ten patients before starting a continuous "white noise" of 90 decibels intensity, and after 29 minutes of noise There was no statistically significant difference in the values of the parameters mentioned above, before and during the period of noise exposure

In modern communities the effects of noise pose a problem of growing importance Complaints about noise are frequent, and the number of people suffering from the result of noise is increasing The noise chiefly emanates from technical appliances, and its intensity is often as high as 100 decibels and more In addition to the noise caused by increasing industrialization we are exposed in our homes to the noise from household machinery, wireless apparatuses etc and on the roads to the noise of mechanized traffic The change from propeller to jet planes creates special noise problems Measures to combat noise are predominantly within the field of the engineer, but to reveal the possible harmful effects of the noise—both mental and physical—is a medical task

The chief physical properties of a sound can be determined by measuring its intensity and frequencies It is often impossible to decide from these qualities whether or not a given sound will be interpreted as noise Noise is usually defined as a sound of unpleasant character (Lehmann, 1955) This definition involves psychological factors although all sounds, regardless of frequency characteristic, appear unpleasant when the intensity is great enough High frequency sounds generally are more apt to create an unpleasant sensation than low frequency sounds A discontinuous sound is usually registered as more unpleasant than a continuous one On the whole self caused sounds are found to be less unpleasant than the sounds caused by others The young motorcyclist often regards the sound from his vehicle as very pleasant indeed while his neighbours consider it a troublesome noise

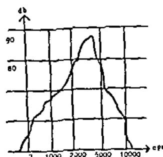


FIG 1 The frequency characteristic of the noise used in the experiment

arterial and at least 2 samples of mixed venous blood in each period The oxygen capacity of the blood was calculated from the haemoglobin which was determined spectrophotometrically (Unicam SP 500) The pressure in the pulmonary artery was recorded before starting the noise and after 5, 10, 15 and 20 minutes of noise The pressure was measured by means of Elema pressure recording apparatus

RESULTS

The results are shown in Tables 2 and 3 There is no statistically significant difference between the values of the oxygen uptake, arteriovenous oxygen difference and cardiac rate before starting the noise and after 20 minutes of noise The mean arithmetical value for the cardiac output was 4 9

TABLE 3 *Hemodynamic data in 10 patients before and during 20 minutes exposure to white noise of 90 db*

Case no	O_2 uptake ml/min		Arteriovenous O_2 difference ml/l		Cardiac output l/min		Cardiac rate		Stroke volume ml	
	Before	During	Before	During	Before	During	Before	During	Before	During
1	230	256	61.4	62.5	3.9	4.1	60	58	65	71
2	221	203	54.0	50.8	4.1	4.0	80	78	51	51
3	231	250	40.0	40.3	5.8	6.2	78	78	74	80
4	276	310	51.8	52.0	5.3	6.0	116	120	46	50
5	222	240	55.0	50.0	4.4	4.8	50	50	88	96
6	205	193	45.5	44.0	4.5	4.4	76	83	59	53
7	288	293	55.3	56.3	5.2	5.2	81	76	64	68
8	232	232	50.0	52.0	4.6	4.5	72	83	64	54
9	300	294	39.0	41.5	7.7	7.1	61	61	129	111
10	296	229	61.5	62.0	3.7	3.7	74	71	[illegible]	52
Arithmetic mean	244	251	50.9	51.2	4.9	5.0	[illegible]	76	68	69
Standard error	11	8	2.4	2.4	0.4	0.4	6	6	7	7

Table 1 *Some characteristics of the 10 patients examined*

Case no	Sex	Age Years	Height cm	Weight kg	Body surface m²	Diagnosis
1	M	53	181	76.0	1.95	Rheumatic heart
2	F	51	162	56.1	1.58	Rheumatic heart
3	F	22	173	71.5	1.88	Atrial septal defect
4	M	63	171	62.6	1.91	Bronchial asthma
5	M	73	179	73.8	1.92	Chronic bronchitis
6	M	67	168	59.6	1.67	Chronic bronchitis
7	M	63	170	73.5	1.84	Chronic bronchitis
8	M	40	171	69.6	1.83	Pulmonary tuberculosis
9	M	60	174	62.7	1.75	Pulmonary tuberculosis
10	M	17	182	61.5	1.80	Acrocyanosis

"white noise" of an intensity of 90 decibels was used. The frequency characteristic of the noise is shown in Fig. 1, where it can be seen that the noise covered a spectrum from about 400 cps to 10–12,000 cps with maximal sound pressure at about 4–5000 cps. Cardiac catheterization was carried out in all cases, with the patient fasting and lying supine.

The cardiac output was determined by Fick's method (1870) immediately before starting the noise and after 20 minutes of noise. The oxygen uptake was measured with a spirometer ('Pulmotest Godard'). Each recording period lasted for at least 8 minutes. The oxygen saturation in the blood was estimated with the oxymeter described by Broch and co-workers (1962). The error of measurement in single tests in routine work with this apparatus is 0.70 %. The oxygen saturation was determined in at least 2 samples of

Table 2 *Mean pressure (mm Hg) in the pulmonary artery before and during exposure to 'white noise' of 90 db*

Case no	Before	Period of exposition			
		5 min	10 min	15 min	20 min
1	18	18			18
2	21	21			25
3	10	12	11	12	11
4	18	18	18	16	14
5	19	19	18	18	18
6	21				17
7	16	18	16	17	17
8	19	17	15	20	13
9	14	14	12	14	17
10	28	28	28	27	30
Arithmetic mean	18.7	18.7	16.9	17.8	18.0
Standard error	1.6	1.6	1.5	2.0	1.8

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l/min with a standard error ± 0.4 before noise, and 5.0 l/min with a standard error ± 0.4 after 20 minutes of noise. The difference is not statistically significant. The difference between the values for cardiac output before and after noise exposure was compared with the difference in values from double determination of the cardiac output in 16 other patients, examined by exactly the same technique except that this group of patients was not exposed to noise. The difference between the two groups was not statistically significant. The mean value for the stroke volume was 68 ml before noise and 69 ml after 20 minutes of noise. The difference is not statistically significant.

The mean value of the mean pressure in the pulmonary artery before starting the noise was 18.7 mm Hg. After 20 minutes of noise the corresponding value was 18.0 mm Hg. There is no statistically significant difference between the results. There was also no significant difference between the original values and those after 5, 10 and 15 minutes of noise.

DISCUSSION

Our investigation confirms the findings of Lehmann and co-workers that cardiac rate is not affected by noise. We were not able to demonstrate that noise causes any change in oxygen uptake, arteriovenous oxygen difference, cardiac output and cardiac stroke volume.

It seems to be a matter of agreement that only minimal changes occur in the systemic blood pressure during a period of noise such as that used in our investigation. Our results demonstrate that the pressure in the pulmonary artery also remained unchanged, as did the cardiac output. It seems therefore reasonable to conclude that the cardiac work does not change during a period of noise. The dissimilarity of our results and those given by Lehmann and co-workers is probably due to differences in technique.

ZUSAMMENFASSUNG

Durch Anwendung von Herzkatheterismus haben wir Sauerstoffaufnahme, Sauerstoffdifferenz in den Pulsadern und Blutadern, Pulsschlag je Minute, Herzschlagvolumen und den Druck in der Lungenpulsader bei zehn Patienten untersucht, sowohl vor Beginn eines ununterbrochenen „weissen Geräusches" von 90 Dezibel Stärke als auch während 20 Minuten Geräusch. Es wurde keine statistisch signifikante Differenz in den Werten der erwähnten Parameter festgestellt, weder vor noch während der Periode, in der die Patienten dem Geräusch ausgesetzt wurden.

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There is now enough experience to present the method and results for the general consideration of trained laryngologists (1963)

Etiological Factors

There are many different types of causative factors These are as a rule conditions that are responsible for complete destruction of the recurrent laryngeal nerve (Jackson) This creates a condition in which the vocal cord rests immobile in a lateral position (abducted, cadaveric, paramedian) In this series of cases the following have been the causes

- Thyroid gland surgery
- Radical neck surgery
- Malignancy within the thorax
- Aneurysm of the aorta with artery replacement
- Coarctation of the aorta with surgical correction
- Pulmonary tuberculosis with thoracic scar formation
- Poliomyelitis
- Chemodectoma involving IX, X and XI cranial nerves in their cervical course
- Trauma to right upper thorax
- Trauma to the neck
- Localized brain damage
- Idiopathic
- Scar replacement of vocal cord after removal for malignancy
- Deformity of cord after excess tumor removal
- Diverticulum of esophagus surgery

Indications

As this technique develops in the hands of more investigators we anticipate that the indications for its use will increase Even at this early stage, Teflon has been implanted in numerous supportive and corrective areas throughout the human body the indications for its laryngeal use comes clear The essential indication is the correction of glottic deformity and abnormal function to re-establish normal function of the glottic valve This implies that air can be held cough and laughter can occur and the breathy hoarse voice with its staccato phrases can return to normal Thus the laterally lying paralyzed vocal cord is the ideal indication for this method The injection of Teflon Dispersion (Teflon ground and mixed with 50 % glycerine by weight) is the best solution of the problem The augmentation of cord size that results moves the medial edge of the cord to the midline The non paralyzed cord may then act with its fellow The glottic valve again has the power and capabilities of complete voluntary closure

The following physiological results flow from this correction The voice is no longer breathy and approaches normal in timber and tone, breath control

GLOTTIC REHABILITATION WITH TEFLON INJECTION—THE RETURN OF VOICE, COUGH AND LAUGHTER

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The injection of Teflon Glycerine mixture into a vocal cord is a procedure that can be learned by any competent laryngologist. It offers a relatively simple and an effective solution to the physiological problems of the non-closing glottis. The method has its most particular application in cases where there is a lateral lying paralyzed vocal cord. It is also useful in building up functioning scars after cordectomy. Occasionally it will help to correct cord deformities.

In the large majority of instances one may anticipate again normal cough, normal ability to strain, markedly improved or normal voice and the ability to laugh again—the attributes of a functioning glottic valve. With this we may anticipate that accidental aspiration should be correspondingly improved.

INTRODUCTION

In 1911, Brunings (1911) reported a method of augmenting the size of a lateral lying paralyzed vocal cord by paraffine injection. The purpose was to reform and rehabilitate the glottis so that the non paralyzed fellow cord could coapt and co operate without air loss, making the glottic valve again functional. This brought back breath control and voice quality, and made effective cough and laughter again possible. In the discussion of this work Killian suggested the risk of tumor formation and, in fact, paraffine injection ultimately became obsolete. For many years the idea remained in limbo. There were occasional efforts at correction. Wallner (1958) implanted cartilage through a thyrotomy incision. Goff (1960) used ground bone; others used diced septal cartilage. All of these methods had a modest measure of success. They were at best complicated and cumbersome and at worst awkward failures. They never caught on.

Thanks to the researches of Arnold, including adequate animal experimentation, a relatively simple method was found. This involved the development of a non reactive injectable mixture of ground Tantalum and glycerine. This was forced thro needle into the paralyzed cord during a well stabilized direct laryngoscopy. Later it was found that a ground Teflon glycerine paste was more practical. This work was established as effective by this author by consistently repeating Arnold's results (1962).

There is now enough experience to present the method and results for the general consideration of trained laryngologists (1963)

Etiological Factors

There are many different types of causative factors These are as a rule conditions that are responsible for complete destruction of the recurrent laryngeal nerve (Jackson) This creates a condition in which the vocal cord rests immobile in a lateral position (abducted cadaveric paramedian) In this series of cases the following have been the causes

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The following physiological results flow from this correction The voi[illegible] no longer breathy and approaches normal in timber and tone breath co[illegible]

TABLE 1 *Results*

Initials	Substance used	Cause	Voice Cough Closure	Sex
1 F B	Tantalum	Tuberculosis	Excellent	Male
2 A T	Teflon	CA of lung	Excellent Reinject 15 mo	Male
3 C S	Teflon	CA of lung	Excellent	Male
4 H P	Teflon	Idiopathic schizophrenic	Excellent (2nd injection)	Male
5 W S	Teflon	Surgery	Slight improvement	Male
6 W C	Teflon	CA of lung	Excellent	Male
7 D L	Teflon	Coarctation of aorta	Excellent	Female
8 J B	Teflon	Chemodectoma cranial IX X, XI	Excellent	Male
9 S M	Teflon	CA of lung	Excellent	Male
10 S B	Teflon	CA of thyroid surgery	Poor to repeat	Female
11 G B	Teflon	Cerebral embolus	Excellent	Female
12 M A	Teflon	Thyroidectomy	Excellent	Female
13 A K	Teflon	Aortic aneurysm?	Excellent	Female
14 W M	Teflon	Poliomyelitis	Excellent	Male
15 F F	Teflon	CA of larynx cordectomy	Excellent	Male
16 A P	Teflon	Idiopathic	Excellent	Male
17 D D	Teflon	Crush chest tracheotomy	Excellent	Male
18 F S	Teflon	Followed pneumonia	Excellent	Female
19 J J	Teflon	Replaced aorta	Excellent	Male
20 M Os	Teflon	Tuberculosis	Excellent	Female
21 G S	Teflon	Cordectomy CA of larynx	(1st sitting) Moderate	Male
22 P B	Teflon	CA of lung	Excellent	Male
23 R K	Teflon	Idiopathic plus plica ventricularis syndrome	Voice unimproved	Female
24 H N	Teflon	Idiopathic (stroke?)	Excellent	Male
25 A K	Teflon	Cordectomy CA	Moderate	Female
26 I K	Teflon	Aortic Aneurysm	Excellent	Male
27 H D	Teflon	Laryngeal injury auto	Excellent	Female
28 S R	Teflon	Injury left cord paralysis	Good	Female
29 M S	Tantalum	CVA (stroke)	Excellent	Male
30 A K	Teflon	Thyroid nodule and surgery	Excellent 1 sec to 12 *seconds sustained* phonation time	Male
31 R G	Teflon	CA left lung	Excellent	Female
32 R M	Teflon	Aneurysm aorta	Excellent	Male
33 J M	Teflon	Diverticulum esophagus (surgery)	Excellent	Female
34 C M	Teflon	Idiopathic	Marked improvement	Male

is such that whole sentences rather than three words can be said after one inspiration There is return of effective cough elimination of aspiration and a return of the sunshine of laughter

In a smaller series of cases we have built up the scar resulting from cor dectomy This tends in the direction of the same result but requires several



April June

FIG 1 Lateral view of tantalum in vocal cord Identical Pattern no drift seen

sittings In some instances too dense a scar limits the effectiveness With comparable limitations cord irregularities and defects can be corrected

Teflon

Teflon $(C_2F_4)_n$ is a product of the research of the Manhattan Project of the Atomic Energy Commission It is one of the most non reactive substances known For this reason it has been used as a graft for artery replacement Animal studies (Arnold 1962) have shown a minimal tissue response Left in tissue for long periods it has not been carcinogenic Its lack of chemical reactivity explains an important industrial use It lines frying pans Such coated pans do not require any grease or butter The preparation is ground so that the particles average between 50 and 100 micra in diameter This is mixed with glycerine as a vehicle to form an injectible paste

Due to these qualities of non reactivity Teflon has not been digested absorbed or extruded as a foreign body Since the average granule size is larger than the diameter of lymphatic drainage channels it remains where it has been placed The fact that it is placed in a passive area is probably also helpful We have expected no drift and we have had none Reinjection was required only three times In one instance there was a slight voice loss after fifteen months (we had never been quite satisfied with the posterior end of the cord here) Perfect voice was returned In the second case our original Teflon was poorly placed on the first attempt Specific observation for drift was made with Tantalum glycerine mixtures This was injected successfully with return of voice Lateral X Ray studies at the end of three [illegible] owed the [illegible]

O [illegible] will last [illegible] at worst *reinjection may prove necessary* in the occasional case Thus far drift migration extrusion or *leeching* have been no problem The *glycerine vehicle is of course soon absorbed*

TABLE 1 *Results*

Initials	*Substance* used	Cause	Voice *Cough* *Closure*	Sex
1 E B	Tantalum	Tuberculosis	*Excellent*	*Male*
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10 S B	Teflon	CA of thyroid surgery	Poor to repeat	Female
11 G B	Teflon	Cerebral embolus	Excellent	*Female*
12 M A	Teflon	Thyroidectomy	Excellent	Female
13 A K	*Teflon*	*Aortic aneurysm?*	*Excellent*	Female
14 W M	Teflon	Poliomyelitis	Excellent	Male
15 F E	Teflon	CA of larynx cordectomy	Excellent	Male
16 A P	Teflon	Idiopathic	Excellent	Male
17 D D	*Teflon*	*Crush chest tracheotomy*	*Excellent*	*Male*
18 E S	Teflon	Followed pneumonia	Excellent	Female
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Fig 4a Lateral lying paralyzed (injected) vocal cord glottis open quiet breathing no phonation *b* injected vocal cord Glottis closed on phonation

cases was this of such degree as to cause any apprehension It was controlled quickly by the use of enzymes to reduce inflammation and corticosteroid therapy

Instruments Required

Laryngoscope preferably anterior commissure type with open side 18 cm or multi purpose type Long needle to traverse laryngoscope at its business end size 19 with Luer lock laryngoscope holder Screw type syringe

Technic

A chest supported direct laryngoscopy assures freedom of action and stability The open side of the laryngoscope creates more room for maneuver and angular introduction of the long needle Accuracy of placement of the Teflon is paramount Only in special circumstances is it placed in the anterior third of the vocal cord Usually two or three implants are made of about 0 2 cc each These are in the substance of the cord implanted at a controlled level assured by the collar near the tip of the needle Implants are placed just lateral to the midline made by the long axis of the cord They are controlled by the turn of the screw of the syringe and observation by the operating

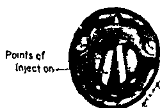


Fig 5

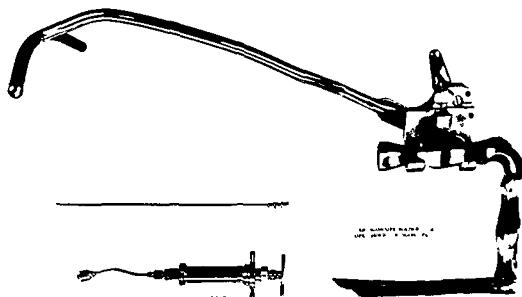


Fig. 2. Instrument used: Laryngoscope holder, open-sided laryngoscope needle, screw-type syringe.

Reactions

About thirty per cent of patients have had a temporary local reaction characterized by edema. This is concentrated mostly in the area of the arytenoid cartilage and the aryepiglottic fold. It is moderate in the vocal fold itself. This may be due to the glycerine or the intratissue pressure. In only three

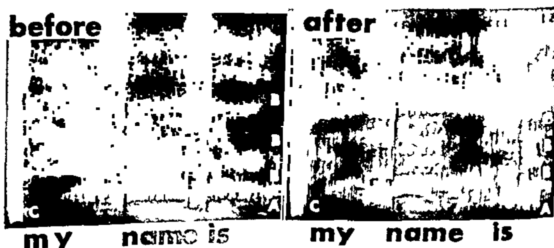


Fig. 3. Spectrograph before and after Teflon injection. A, Basic tone. B, parallel harmonic. C, individual vibration.

THE FREQUENCY OF SOCIAL HEARING HANDICAPS IN DENMARK

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At the Danish State Hearing Centres all patients with deficient hearing are entitled to otological audiological examinations and if needed they are fitted with commercial type hearing aids free of charge These hearing aids should be returned to the institutions after death The case records of 1470 deceased persons thus fitted with hearing aids have been examined covering the period January 1959 May 1961 A statistical analysis shows that 1 2 % of the population are fitted with hearing aids (for those older than 15 years 2 9 %) Graphs are presented of the distribution as to age and diagnosis These figures are used to establish a prognosis for the future need in rehabilitation of the hard of hearing population

The frequency of hearing defects is a decisive factor in future planning of social rehabilitation work for the hard of hearing persons

Various methods have been used in order to obtain figures that are valid in such planning Beasley (1940) interviewed 700 000 households from city districts in the U S A —9324 of those questioned were examined clinically He found that 1 3 % of the male population was hard of hearing For females the percentage was 1 2 All stages of hearing defects were included in these figures

Bentzen & Jelnes (1955) proceeded in a different way 1569 consecutive patients admitted to a major regional hospital in Denmark were interviewed with regard to the occurrence of deficient hearing in persons belonging to the household so that the investigation covered a total of 5000 persons—all individuals with a presumed hearing loss were submitted to audiometric testing The authors came to the conclusion that 6 % of the population was socially handicapped due to defective hearing

Wilkins (1950) interviewed 31 899 persons or 0 07 % of the population in the United Kingdom and found that the number of hearing handicapped in Great Britain was about 4 %

The disagreement between these figures (1 25 % 4 %–6 %) is so considerable that further study seems indicated

Since 1951 Denmark has been covered by State Hearing Rehabilitation Centres where all Danish citizens are entitled to free audiological examinations and if needed fitted with commercial type hearing aids These are given free of charge as a loan and should be returned to the institution after the death of the patient or when otherwise they become obsolete

surgeon As the work is done under local anesthesia the patient s attempts at phonation tell the story to the eye of the examiner

Lateral implantation becomes subglottic Medial implants raise bumps that create the voice equivalents of neoplasms The accuracy demands a stabilized laryngoscope Prior practice on cadaver larynxes should be considered mandatory

ZUSAMMENFASSUNG

In diesem Artikel wurde uber eine Reihe von 35 Patienten berichtet Die Mehrzahl dieser Patienten zeigte ein lateral liegendes gelähmtes Stimmband Um dieser Lähmung entgegenzuwirken wurde eine Paste, eine Mixtur aus Teflon und Glyzerin in das gelähmte Stimmband durch ein Laryngoskop injiziert mit Hilfe einer schraubenartigen Spritze und einer langen Nadel Dies erzeugte eine Zunahme im Umfange des Stimmbandes Der Rand des gelähmten Stimmbandes wurde dadurch gegen die Mitte verschoben Auf diese Weise wurde eine fast normale Funktion der Glottis wiederhergestellt, welche ihrerseits den Luftverlust kontrollierte Das ermoglichte eine nahezu normale Stimme Eine normale Husten und Lachfunktion wurde auch erzielt

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TABLE 1 *Distribution of 1420 deaths among users of hearing aids by age and diagnosis*

	50	50–54	55–59	60–64	65–69	70–74	75–79	80–84	>85	Total
Otitis seqv	9	9	8	20	32	63	58	61	31	291
Otosclerosis	2	2	5	17	15	22	33	25	16	137
DNA senilis	—	—	—	3	14	63	140	209	237	666
DNA meneriformis	—	—	—	—	2	2	2	2	—	8
DNA here l t / DNA cong	1	—	2	3	6	14	10	9	5	50
DNA prof	—	—	2	7	9	22	24	17	9	90
DNA typus inc	6	2	6	10	31	26	40	37	20	178
Total	18	13	23	60	109	212	307	360	318	1420

from whom hearing aids were not returned and should be the true figures The graph is rather even except for the youngest age groups Here the absolute figures however, are small and these irregularities have been disregarded in the drawing of the final graph The same method of calculation has been applied to the diagnostic sub groups (Fig 3) Here again the figures are small and the graphs become somewhat irregular In all groups there is a general trend towards an increase with age This is thought to be due to a superimposition of presbycusis In the oldest groups there is a decrease of all diseases except presbycusis probably caused by a tendency towards less differentiation in the medical diagnosis and an acceptance of age as the main causative factor

When the age distribution of the Danish population is taken into account the overall incidence of hearing handicaps becomes 1 2 % (for those older than 45 years 2 9 %) and with a population of 4 6 mill, a total of 55 000 persons should wear hearing aids

From Fig 2 it is possible to estimate the future number of patients for the

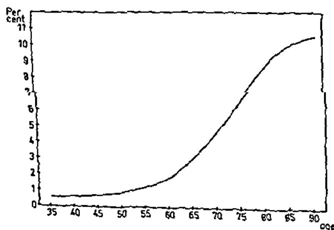


FIG 2 Percentage of hard-of hearing by age as judged by the use of hearing aids

15 61*96

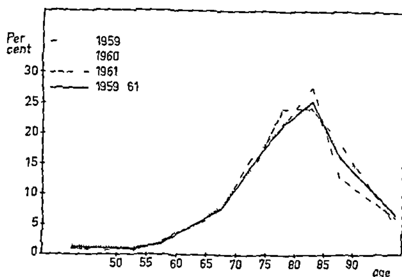


Fig. 1. Age distribution of the hard of hearing among all deaths in capital area 1959–1961.

The experience accumulated in such institutions should be of considerable interest when attempts are made to establish the true rate at which social hearing handicaps occur in a population.

A simple enumeration of all new applicants is unsatisfactory from a statistical point of view and does not give information that can be used in a prognosis for future needs. Instead we have perused the case histories for all patients that died within a certain area during a certain period of time. Our knowledge about the death of a patient derives from the obligation of the family to return hearing aids. Thus the percentage at which this obligation was fulfilled becomes critical for the study and had to be checked.

The material consists of 1420 hearing aid candidates who died in the years 1959, 1960 and the first half of 1961 within Copenhagen and the three surrounding counties with a total population of ca. 1.5 mill.

The total number of deaths in this area in the year 1961 was 15,338 and our material constitutes approximately 3.6 % of all deaths when calculated on a yearly basis. For three of the months under study (January, April and July 1961) we compared the statistical lists over all deceased persons in the city of Copenhagen with the files of the hearing centre. 98 were found to possess a hearing aid at the time of death and during each of the three months only ⅔ of the hearing aids belonging to these (a total of 65) had been returned to the institution. This figure is considered to be representative for the whole period of 2½ years and we found nothing which indicated that the age distribution of those from whom the hearing aids were not returned differed from the rest of the material.

The whole material is presented in Table 1 and Fig. 1 shows the age distribution for each of the three years. From these graphs and from the known death rates of the whole population in various age groups it is possible to calculate the incidence of hearing handicaps according to age (Fig. 2). The percentages given here have been corrected for those patients

survey the uncertainty introduced by this factor in all probability has been reduced to a minimum

The number of hearing aids delivered from all Danish hearing centres are as follows

1961—13 536
1962—14 452

These figures are actually a little too high as for administrative reasons one patient is registered twice if during a control period of one month the first hearing aid turns out to be unsatisfactory and consequently he is fitted with another At a stock taking in September 1963 of index cards for hearing aids it was found that the State Hearing Centre of Copenhagen had delivered about 28 000 hearing aids within a district including 48 % of the population This amount corresponds well with the estimated figure of 55 000 patients found above as a small number of unknown hard of hearing persons have been equipped with an extra apparatus as a spare apparatus and a small number have got two hearing aids for binaural hearing On the whole the figures seem to corroborate the validity of the present statistical method of survey

A point of special interest is the period of life in which hearing handicaps begin Figs 1 2 and 3 give the age at which hearing aids are used and frequently there will be a long interlude in which the patient is aware of a hearing handicap but still tries to get along unaided From the case histories we have taken the patients own statements concerning this question The information must be accepted with considerable reservation and we have hesitated to give detailed figures still we will like to give a rough estimate

In otosclerosis only few cases begin before the age of 20 Each of the following three 10 year spans accounted for 1/5 and the remainder began after the age of 50 1/3 of the non otosclerotic conductive hearing disorders were present before the age of ten and rather surprisingly 1/4 did not notice hearing problems until after the age of 60

DNA senilis appeared with 1/3 before the age of 70 and 1/3 between 70 80 Of the unclassified neurolabyrinthopathies 40 % dated back to before the age of 50 From 50 60 and 60 70 there were 25 % new cases in each group

The heredito congenital diseases showed a very similar pattern Professional DNA gave symptoms for 1/3 in the years 50 60 From 60 70 there were added another 1/3

ZUSAMMENFASSUNG

In den staatlichen dänischen Hörzentren können sich alle Patienten mit reduziertem Gehör einer otologisch audiologischen Untersuchung unterziehen und wenn Bedarf dafür besteht, werden ihnen kostenfrei sich im Handel befindliche Hörgeräte zur Verfügung gestellt Diese Hörgeräte sollen bei Todesfall den Hörzentren zurückgegeben werden Man hat die Krankengeschichten von 1490 schwerhörigen Patienten die in der Periode Januar 1959 bis Mai 1961 gestorben sind und

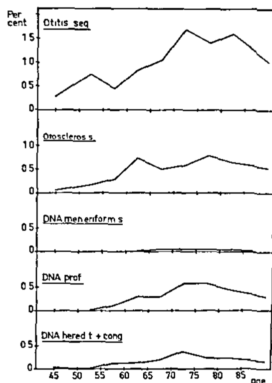


Fig. 3*a*

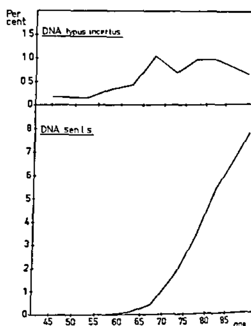


Fig. 3*b*

Fig. 3*a*. Percentage of hard of hearing by age and diagnosis.
Fig. 3*b*. Percentage of hard of hearing by age and diagnosis.

area under study. Each year there will be 1235 new cases (1085 over the age of 45, and 150 between 15 and 45 years of age). With deduction of 550 deaths the clientele should increase at a rate of 685 a year. The general policy has been to re-examine patients every 5 years. If the age distribution of all new cases is taken into account 1235 new cases will necessitate 2770 re-examinations, and the total number of examinations should be around 4000 a year.

Our area includes only 1/3 of the country, and the estimated capacity for the whole of Denmark at the present stage should accordingly be 12,000.

This is a minimal figure and several factors tend to cause a steady increase. Thus the remarkable technical improvement of hearing aids makes the 5-year re-examination rate more or less obsolete. To all probability these improvements will gradually overcome the difficulties with the large group of borderline cases, where with present means hearing aids often cause more discomfort than help.

Furthermore there remains a certain sale of hearing aids from private dealers. This is more or less a psychological phenomenon, and for several reasons this sale is expected to decline. At present the private market accounts for about 1/4 of all hearing aids used. Experience has shown that a considerable number of those patients who buy their own hearing aids sooner or later seek contact with the hearing centre, and with the present method of

RECONSTRUCTION OF THE OSSICULAR CHAIN BY INCUS PROSTHESIS

A Preliminary Report

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University of Bergen

The author describes a new method for reconstructing the ossicular chain by using a polyethylene prosthesis to replace a damaged incus.

In chronic otitis media it is usually the long crus of the incus which is destroyed first, and disrupture of the ossicular chain in chronic otitis media occurs most frequently between the incus and the stapes. Destruction of the stapes is next in frequency. The malleus is the most resistant of the ossicles against chronic infection. In 190 ears operated on for chronic otitis media in Haukeland Hospital it was found that the long crus of the incus was destroyed in 74.2% (141 ears). The chain was intact in 49 cases. In 51 of the 141 cases where the long crus of the incus was destroyed there was also complete or partial destruction of the stapes.

The long crus of the incus is the weak link of the ossicular chain and also its central point, for if the long crus is intact it is relatively easy to reconstruct the mechanical system of the ear. Surgery of the stapes has taught us that replacement of the stapes by a satisfactory prosthesis is a comparatively simple matter.

In subluxation of the incus, for example after earlier mastoidectomy or head injury, it is possible to obtain a functionally good mechanical system by merely replacing the incus in its proper position. It also happens in stapedectomies that the incus is subluxated without mechanically influencing sound transmission. The author has operated on several ears where there was subluxation of the incus following earlier mastoidectomy and obtained full closure of the bone air gap by merely repositioning the incus. The malleoincudal joint therefore need not be completely intact to insure satisfactory function of the mechanical system of the ear. It is sufficient if the incus and the head of the malleus are in close enough proximity for movement of the malleus to be transmitted to the incus.

These observations led the author to the thought about a year ago, that it might be feasible to construct a prosthetic incus which could fill the breach in the chain.

denen mit Horgeräten geholfen wurde, durchgearbeitet Eine statistische Analyse zeigt, dass 1,2 % der Bevolkerung mit Horgeräten ausgestattet ist (uber 45 Jahre alt 2,9 %) Es sind Kurven gezeigt uber Alters und Diagnoseverteilung Die Kurven sind angewendet worden zur Ausarbeitung einer Prognose fur den zukunftigen Bedarf der Rehabilitierung der schwerhorigen Bevolkerung

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The State Hearing Centre, Copenhagen Denmark

Received September 30 1963



Fig 1 *The incus in position* In the preparation the bridge has been removed in order to provide an unobstructed view

Fig 2 A preparation in which the *bridge* has been toned down as done in actual operation

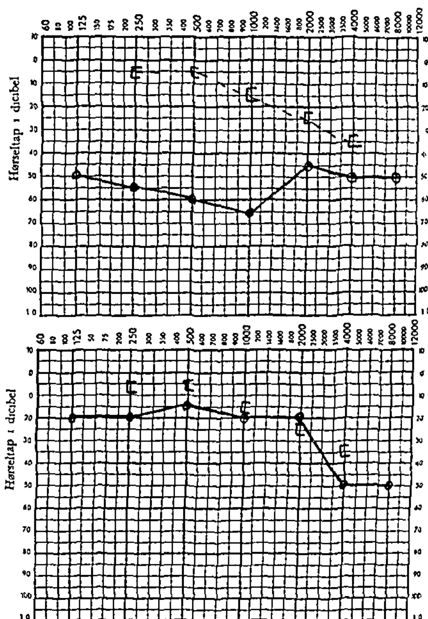


Fig. 4 The pre- and post-operative audiogram of a patient in whom both the incus and stapes were destroyed

In the literature many suggestions are offered for bridging the gap in the chain when the long crus of the incus is more or less destroyed. Most commonly it is suggested to use stainless steel wire between the remaining part of the long crus of the incus and the stapes or to connect the shaft of the malleus directly with the stapes in the same way. Other workers have placed the body of the incus on the head of the stapes in order to get a larger area of contact between the drum and the stapes. Still others have used a polyethylene strut on the top of the stapes with the end against the drum star shaped. The author has tried all these methods without obtaining predictable results.

The incus varies in size and shape from one ear to the other but not to such a degree that one could not use a suitable prosthesis with only minor adjustments during operation to ensure a satisfactory fit. This is especially the case if the prosthesis is made of a material that can be reshaped when heated. It is therefore only natural that a polyethylene material was chosen for incus prosthesis. Stapedectomy *ad modum* Shea has given us the experience that polyethylene is well tolerated in the middle ear. But we are also trying a prosthesis made out of stainless steel.

The connection between the incus and the head of the malleus must be such that the incus lies securely against the head of the malleus. At the same time it must be relatively easy to place the prosthetic incus in position. This has been the most difficult problem to solve. For the present we are using stainless steel wire clips which can be bent around the head of the malleus without destroying the ligaments. The prosthesis for the incus is cast so that the shape is like that of the original bone. The lenticular process of the incus prosthesis and the stapes are connected by means of a small piece of polyethylene tube.

In cases where the stapes is destroyed it can be replaced by a polyethylene strut from the lenticular process of the prosthesis to the oval window. The operation is performed like a usual tympanoplasty. The bridge is not removed but thinned down so that one has a good view of the ossicles. When the prosthesis has been placed in position the defects in the tympanic membrane are repaired by using temporal fascia. The cavity in the mastoid bone is filled with a flap of temporal muscle.

It is now six months since we started using incus prosthesis after the method outlined above. No instances of foreign body reaction in the middle ear have occurred in this period and the results judged in terms of improved hearing have been encouraging.

It is still necessary to widen our experience and gain more knowledge by applying new methods but in our opinion this appears in principle to be a good solution to the problem of reconstructing the ossicular chain. As we only have operated on 20 ears to the present, this publication must obviously be regarded as of preliminary nature. No reference can [illegible]

[illegible] and sufficient time for observing cases already operated on must of necessity be allowed before the assessment of results can be finally published.

The E.N.T. Clinic, Haukeland Sykehus,
Bergen, Norway.



FIG 3 A photograph of an actual operation in progress after the prosthesis has been secured but before the temporal fascia has been brought into position to cover the defect in the tympanic membrane Both the long crus of the incus and the stapes were destroyed

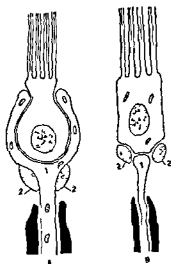


Fig 1 *A* Cellule du type I *1* Terminaison nerveuse en forme de calice *2* Terminaisons nerveuses pourvues de nombreuses formations granuleuses — *B* Cellule du type II *1* Terminaison nerveuse qui contient une petite quantité de granulations *2* Terminaisons nerveuses pourvues de nombreuses formations granuleuses (d après Wersäll 1960 modifiee)

produit la disparition d un système de fibres nerveuses très minces situees au dessous des cretes acoustiques et des plages otolithiques

Petroff (1955) affirme que ces fibres efferentes ont un cours croise, parce qu une incision mediane du planche du IV ventricule produit la disparition de ce système de fibres dans les deux labyrinthes

En 1958 Rasmussen & Gacek et en 1960 Gacek ont publie les resultats de leur recherches accomplies chez le chat et chez le chincilla Les Auteurs ont etudie le phenomene de la degenerescence des fibres nerveuses produit par la destruction electrolytique de petites zones du bulbe au niveau des noyaux vestibulaires ou par l incision sagittale du planche du IV ventricule en de differents points

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Gacek (1960) pense en effet qu ils existent seulement des fibres efferentes directes et que le noyau vestibulaire lateral soit leur probable point d origine

Les resultats obtenus par la methode de la chromatolyse de Nissl apres labyrinthectomie unilaterale n ont pas permi a Gacek (1960) d etablir exactement le noyau d origine des fibres vestibulaires efferentes

En 1959 Carpenter Bard et Alling et en 1960 Carpenter ont publie les resultats d une serie de recherches faites chez le chat et le singe par la methode de la chromatolyse de Nissl apres labyrinthectomie unilaterale ou apres section de la VII[e] et de la VIII[e] paire

Selon ces Auteurs le noyau du toit le noyau vestibulaire medial le noyau

L'INNERVATION EFFÉRENTE DES RÉCEPTEURS VESTIBULAIRES

GIOVANNI ROSSI
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En résumant les données de la littérature et les résultats de ses recherches morphologiques et fonctionnelles, l'Auteur expose nos actuelles connaissances à propos de l'innervation efférente des récepteurs vestibulaires.

De récentes recherches anatomiques, histochimiques, expérimentales et électrophysiologiques ont démontré l'existence de fibres vestibulaires à cours centrifuge, qui ont leur noyau d'origine dans le bulbe. On doit compléter les résultats de ces recherches par les renseignements que la microscopie électronique nous a donnés dans ces dernières années à propos de la morphologie des récepteurs vestibulaires.

Les recherches de Wersäll (1954–1956) ont en effet démontré l'existence dans les crêtes acoustiques du cobaye, du chat et du rat, de deux types de cellules ciliées.

Les cellules du type I, selon la classification de Wersäll (1954, 1956), ont la forme d'une fiasque et leur base est contenue dans une terminaison nerveuse en forme de calice qui contient des formations granuleuses en petite quantité (Wersäll 1956, Smith 1956). A l'extérieur de ce calice on observe d'autres terminaisons nerveuses, qui paraissent au contraire pourvues de nombreuses formations granuleuses (Engström 1958).

Les cellules du type II, selon la classification de Wersäll (1954, 1956), ont une forme cylindrique, mais leur partie basale n'est pas contenue dans une terminaison nerveuse en forme de calice. Au niveau de la partie basale des cellules de ce type il y a des terminaisons nerveuses qui contiennent une petite quantité de granulations et des terminaisons nerveuses pourvues de nombreuses formations granuleuses, du même type de celles observées à la base des cellules du type I (Engström 1958, Wersäll 1960) (fig. 1). L'existence de ces deux types de terminaisons nerveuses (du type granuleux et du type non granuleux) a fait faire à Engström (1958) l'hypothèse que les terminaisons nerveuses du type granuleux, qui ont des caractéristiques morphologiques de terminaisons extra-synaptiques (Engström 1958, Wersäll 1960), appartiennent aux fibres vestibulaires efférentes, dont Petroff avait signalé l'existence la première fois en 1955.

Cet auteur avait en effet observé, chez le chat et le singe, que la section de la VIII° paire ou une incision médiane du plancher du IV ventricule

Conférence prononcée le ... 1963 à la Società di Scienze Mediche e Naturali dell'Università di Sassari.

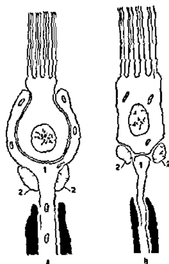


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La preuve de la nature efferente de ces fibres positives à la reaction de Koelle et Friedenwald pour l'acetylcholinesthérase a été donnée par Ireland & Farkashidy (1961). Ces Auteurs ont en effet démontré chez le chat, que la section du rameau vestibulaire de la VIII^e paire cause la disparition de l'activité d'acetylcholinesthérase à niveau des crêtes acoustiques et des plages otolithiques.

En 1962 Hilding & Wersäll en faisant usage *de la réaction de Koelle et* Friedenwald dans une étude accomplie par le microscope électronique, ont pu localiser exactement les zones de positivité à cette réaction. Ces intéressantes recherches ont démontré que, dans les crêtes acoustiques, la réaction de Koelle et Friedenwald pour l'acetylcholinesthérase est positive exclusivement à niveau des terminaisons nerveuses du type granuleux qui sont situées à la base soit des cellules du type I, soit *de celles du type II*.

L'existence de fibres efferentes dans le nerf vestibulaire a été confirmée par les recherches électrophysiologiques de Sala (1962) et de Schmidt (1963).

Sala (1962) en stimulant par des ondes carrées le planché du IV ventricule du chat à niveau de la zone où se trouvent les noyaux vestibulaires a observé l'apparition dans le nerf vestibulaire du *côté opposé d'un potentiel à pointe* généralement monophasé positif de forme semblable aux potentiels spontanés. L'intervalle entre la stimulation et l'apparition du potentiel dans le nerf vestibulaire était de 22–32 m sec.

Schmidt (1963) a pu démontrer l'existence dans la « Rana *pipiens* », d'impulsions efferentes qu'il a pu dériver de l'extrémité du nerf détaché *de l'ampoule* du saccule de l'utricule et de la lagène. *L'apparition de ces impulsions efferentes* qui normalement n'existent *pas*, *était* produite par la *stimulation d'une* ampoule ou par la stimulation de certaines *terminaisons nerveuses* extralabyrinthiques que Schmidt (1963) n'a pu exactement identifier.

L'étude systématique de l'innervation efferente des *recepteurs vestibulaires* a été commencée par Rossi *en* 1960 à travers des recherches hystochimiques et continuée en suite à travers *des recherches* embryologiques (1962) des recherches anatomiques faites avec *la* collaboration de Cortesina (1962*a*, *b* 1963, 1964) et des *recherches expérimentales* conduites avec la collaboration de Voena, Buongiovanni, Cortesina (1964).

Le point de départ de ces recherches a été fourni par une remarque faite par Rossi en 1960 : on peut aisément différencier les fibres efferentes cochléaires qui forment le faisceau spiral intraganglionnaire, des fibres afferentes parce que les fibres *efferentes cochléaires* sont positives à la réaction de Koelle et Friedenwald pour l'acetylcholinesth*érase*.

Rossi se proposa par conséquent de vérifier si cette différence vis à vis de la réaction de Koelle *et Friedenwald* pour l'acetylcholinesthérase se produisait aussi pour les fibres *afferentes* et pour les fibres efferentes vestibulaires.

En 1962 Rossi a étudié *la localisation* de l'acetylcholinesterase *au cours* du développement de *l'oreille* interne *du rat* ave*c et il* a pu constater, par des *contrôles* faits par la méthode de l'argent réduit selon Cajal que l'apparition

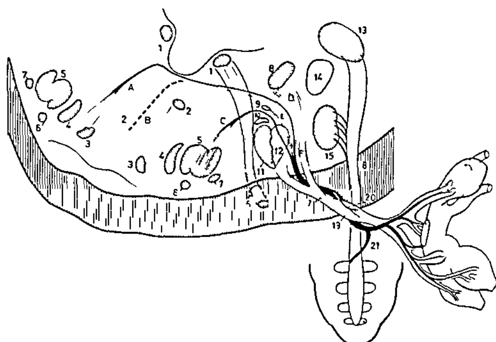


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vestibulaire supérieur et une partie du noyau vestibulaire inférieur donnent naissance à des fibres vestibulaires efférentes. Les fibres qui ont leur origine du noyau du toit seraient pour la plupart croisées, tandis que celles qui ont leur origine des noyaux vestibulaires susmentionnés seraient pour la plupart directes.

A côté de ces études accomplies par la méthode anatomique, il faut rappeler la recherche histochimique de Dohlman, Farkashidy & Salonna (1958). Ces Auteurs, en faisant usage de la technique de Koelle & Friedenwald (1949) pour l'acétylcholinesthérase, ont démontré l'existence de fibres nerveuses pourvues d'activité d'acétylcholinesthérase au dessous du neuroépithélium des crêtes acoustiques et des plages otolithiques du pigeon.

Ces fibres existeraient seulement à niveau des crêtes acoustiques et des plages otolithiques et seraient indépendantes des vaisseaux. Pour ces raisons et en vertu de l'activité d'acétylcholinesthérase dont ces fibres paraissent pourvues, Dohlman, Farkashidy & Salonna (1958), Dohlman (1960) sont de l'avis qu'il s'agit de « fibres cholinergiques efférentes ».

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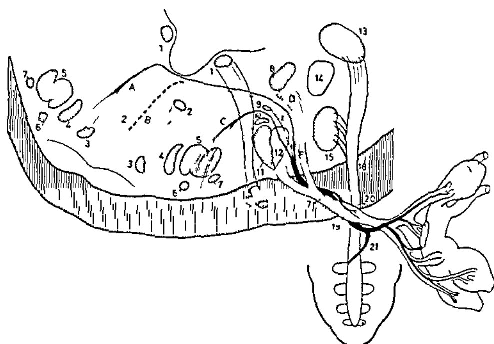


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A côté de ces études accomplies par la méthode anatomique il faut rappeler la recherche histochimique de Dohlman, Farkashidy & Salonna (1958). Ces Auteurs, en faisant usage de la technique de Koelle & Friedenwald (1949) pour *l'acetylcholinesthérase ont démontré l'existence de fibres nerveuses* pourvues d'activité d'acetylcholinesthérase au dessous du neuroépithélium des crêtes acoustiques et des plages otolithiques du pigeon.

Ces fibres existeraient seulement au niveau des crêtes aucoustiques et des plages otolithiques et seraient indépendantes des vaisseaux. Pour ces raisons et en vertu de l'activité d'acetylcholinesthérase dont ces fibres paraissent pourvues, Dohlman, Farkashidy & Salonna (1958), Dohlman (1960) sont de l'avis qu'il s'agit de « fibres cholinergiques efférentes ».

De ce noyau forme dans le cobaye par 120 150 cellules prend naissance un faisceau de fibres efferentes que Rossi & Cortesina (1962*a* *b* 1963 1964) ont denomme « *faisceau vestibulaire efferent direct ventral* »

Le second faisceau de fibres efferentes qui relient le bulbe au labyrinthe membraneux posterieur prend naissance du noyau vestibulaire lateral dans sa partie anterieure et inferieure Ce faisceau de fibres efferentes vestibulaires dont Rossi & Cortesina (1962*a* *b* 1963) ont demontre pour la premiere fois l origine et le trajet forme le « *faisceau vestibulaire efferent direct dorsal* »

Dans l innervation efferente du labyrinthe membraneux posterieur a part aussi selon les donnees obtenues par les recherches de Rossi & Cortesina (1962*a* *b* 1963 1964) un faisceau de fibres qui prend naissance de cellules de la substance reticulaire du pont et de la protuberance situees aux cotes du raphe median (*faisceau reticulo cochleaire et vestibulaire direct*) (fig 2)

Les recherches de Rossi & Cortesina n ont pas demontre l existence de fibres efferentes vestibulaires croisees Rossi & Cortesina (1962*a* *b* 1963 1964) ont aussi confirme les resultats obtenus par Ireland & Farkashidy (1961) Ils ont pu en effet demontrer que l activite d acetylcholinesthérase qui normalement existe a niveau des cretes acoustiques et des plages oto lithiques est en rapport avec les fibres vestibulaires efferentes Rossi & Cortesina (1962*a* *b* 1963 1964) dans une derniere serie de recherches ont en effet observe qu une incision sagittale a niveau de l angle lateral du planche du IV ventricule qui coupe les fibres vestibulaires efferentes cause la disparition de l activite d acetylcholinesthérase des cretes acoustiques et des plages otolithiques

Toutes les recherches ci dessus mentionnees accomplies sur de differentes especes d animaux ont demontre l existence d un systeme de fibres nerveuses efferentes qui ont leur noyau d origine dans le bulbe et qui relient le bulbe aux recepteurs vestibulaires

De ces recherches on peut en outre deduire que les expansions les plus peripheriques des fibres vestibulaires efferentes sont situees a la base des [illegible] cretes acoustiques qu elles [illegible] que la presence de cet [illegible] integrite des fibres vestibulaires efferentes

La presence d acetylcholinesthérase dans un point bien defini de l ensemble forme par la cellule ciliee par la fibre afferente et par celle efferente suppose l existence a ce niveau d un mecanisme de transmission de l impulsion nerveuse sur la base du systeme acetylcholine cholinacetylase–acetylcholinesthérase en rapport avec les fibres efferentes (fig 3)

D apres cette premisse Rossi Buongiovanni Cortesina et Voena (1964) dans une recherche preliminaire ont etudie les effets produits sur la fonction vestibulaire par l introduction par voie carotidienne du diisopropylfluoro phosphate (DFP) substance pourvue d activite anticholinesthérasique Ces recherches ont ete executees chez le lapin dont l innervation vestibulaire

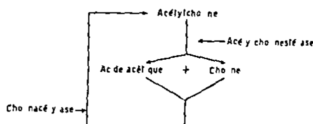


Fig. 3

de la positivité à la réaction de Koelle et Friedenwald pour l'acétylcholinesthérase au niveau de chacune des structures neurosensorielles du labyrinthe membraneux est toujours précédée par l'apparition de la positivité à cette réaction dans un faisceau de fibres nerveuses qui gagne chaque structure neurosensorielle.

Les fibres vestibulaires afférentes se conduisent négativement à la réaction de Koelle et Friedenwald pour l'acétylcholinestérase. Pour ce qui concerne le labyrinthe membraneux postérieur on a pu démontrer (Rossi 1962, Rossi & Cortesina 1962*a*, *b*, 1963) que dans les rameaux terminaux du nerf vestibulaire du cobaye on retrouve des fibres positives à la réaction de Koelle et Friedenwald pour l'acétylcholinestérase seulement après la naissance.

Dans d'autres recherches Rossi & Cortesina (1962*a*, *b*, 1963, 1964) ont *appliqué la réaction de Koelle et Friedenwald pour l'acétylcholinesthérase* à l'étude du bulbe du cobaye et du lapin.

Se rappelant de la nette positivité à cette réaction des seules fibres vestibulaires efférentes, Rossi et Cortesina ont retenu de pouvoir obtenir par cette étude des données utiles à la connaissance de l'origine, du trajet et des rapports des fibres vestibulaires efférentes.

Les résultats obtenues par cette recherche ont été contrôlés par d'autres séries de recherches exécutées selon les données classiques de l'anatomie microscopique du système nerveux centrale: coloration de Nissl, méthode de l'argent réduit selon Cajal, méthode de chromatolyse de Nissl.

A travers cette série de recherches anatomiques, histochimiques et expérimentales Rossi & Cortesina (1962*a*, *b*, 1963, 1964) ont pu démontrer l'existence de deux faisceaux de fibres efférentes qui relient le bulbe au labyrinthe membraneux postérieur.

Le premier de ces deux faisceaux prend naissance d'un petit noyau dont Rossi et Cortesina ont signalé pour la première fois l'existence et qu'ils ont dénommé *noyau vestibulaire interposé*. Ce noyau se trouve dans une position dorsale par rapport à la partie supérieure du noyau vestibulaire inférieur et dans une position ventrale par rapport à la partie inférieure du noyau vestibulaire latéral. Ce noyau n'est pas identifiable morphologiquement ni avec les quatre noyaux vestibulaires principaux ni avec les autres groupes cellulaires jusqu'ici décrits qui ont avec les noyaux principaux des étroites relations topographiques.

De ce noyau formé dans le cobaye par 120-150 cellules prend naissance un faisceau de fibres efférentes que Rossi & Cortesina (1962*a*, *b*, 1963, 1964) ont dénommé « *faisceau vestibulaire efférent direct ventral* ».

Le second faisceau de fibres efférentes qui relient le bulbe au labyrinthe membraneux postérieur prend naissance du noyau vestibulaire latéral dans sa partie antérieure et inférieure. Ce faisceau de fibres efférentes vestibulaires dont Rossi & Cortesina (1962*a*, *b*, 1963) ont démontré pour la première fois l'origine et le trajet forme le « *faisceau vestibulaire efférent direct dorsal* ».

Dans l'innervation efférente du labyrinthe membraneux postérieur a part aussi, selon les données obtenues par les recherches de Rossi & Cortesina (1962*a*, *b*, 1963, 1964) un faisceau de fibres qui prend naissance de cellules de la substance réticulaire du pont et de la protubérance situées aux côtés du raphé médian (*faisceau réticulo-cochléaire et vestibulaire direct*) (fig. 2).

Les recherches de Rossi & Cortesina n'ont pas démontré l'existence de fibres efférentes vestibulaires croisées. Rossi & Cortesina (1962*a*, *b*, 1963, 1964) ont aussi confirmé les résultats obtenus par Ireland & Farkashidy (1961). Ils ont pu en effet démontrer que l'activité d'acétylcholinesthérase qui normalement existe a niveau des crêtes *acoustiques et des plages otolithiques est en rapport avec les fibres vestibulaires efférentes*. Rossi & Cortesina (1962*a*, *b*, 1963, 1964) dans une dernière série de recherches ont en effet observé qu'une incision sagittale a niveau de l'angle latéral du plancher du IV ventricule qui coupe les fibres vestibulaires *efférentes cause la disparition de l'activité* d'acétylcholinesthérase des crêtes acoustiques et des plages otolithiques.

Toutes les recherches ci-dessus mentionnées accomplies *sur de différentes* espèces d'animaux ont démontré l'existence *d'un système de fibres nerveuses efférentes* qui ont leur noyau d'origine dans le bulbe *et qui relient le bulbe aux récepteurs vestibulaires*.

De ces recherches on peut *en outre déduire* que les expansions les plus périphériques des fibres vestibulaires *efférentes* sont situées à la base des

crêtes acoustiques qu'elles

que la *présence* de cet

... est en rapport avec l'intégrité des fibres vestibulaires efférentes.

La présence d'acétylcholinesthérase *dans un point bien défini* de l'ensemble formé par la cellule ciliée *par la fibre* afférente et par celle efférente suppose l'existence à ce *niveau d'un* mécanisme de transmission de l'impulsion nerveuse sur la *base du* système acétylcholine-cholinacétylase-acétylcholinesthérase *en rapport avec les* fibres efférentes (fig. 3).

D'après cette *prémisse* Rossi, *Buongiovanni*, Cortesina et Voena (1964) dans une recherche *préliminaire ont étudié* les effets produits sur la fonction vestibulaire par l'*introduction par voie* carotidienne du diisopropylfluorophosphate (DFP) *substance pourvue d'activité* anticholinesthérasique. Ces recherches ont été exécutées chez le *lapin* dont l'innervation vestibulaire

efférente, d'après des recherches préliminaires de Rossi & Cortesina (1964) est identique à celle du cobaye.

L'action du DFP a été étudiée par enregistrement électronystagmographique et a été contrôlée au moyen de la réaction de Koelle et Friedenwald pour l'acétylcholinestérase, qui a été exécutée sur le bulbe et sur les crêtes acoustiques.

A travers ces recherches Rossi, Buongiovanni, Cortesina & Voena (1964) ont pu confirmer que l'introduction du DFP par voie carotidienne déclenche chez le lapin un syndrome vestibulaire (*the adversive syndrome*) qui avait été déjà étudié en 1949 par Freedman & Himwich.

Les contrôles histochimiques ont démontré que la positivité à la réaction de Koelle et Friedenwald pour l'acétylcholinestérase avait sensiblement diminué dans la moitié du bulbe du même côté de la carotide commune dans laquelle on avait fait l'injection du DFP.

En particulier Rossi, Buongiovanni, Cortesina & Voena (1964) ont pu observer la disparition unilatérale de la positivité à la réaction de Koelle et Friedenwald pour l'acétylcholinestérase au niveau des fibres vestibulaires efférentes et des crêtes acoustiques. Par conséquent ils pensent que, *même* sans pouvoir exclure l'existence d'autres mécanismes, la pathogénie du syndrome vestibulaire produit par l'introduction par voie carotidienne du DFP soit liée, *au moins en partie, à la réduction unilatérale de la quantité* d'acétylcholinestérase et à la conséquente accumulation d'acétylcholine qui se vérifie, dans ces conditions expérimentales, au niveau des fibres vestibulaires efférentes et du neuroépithélium des crêtes acoustiques.

La disparition de la positivité à la réaction de Koelle et Friedenwald pour l'acétylcholinestérase au niveau des récepteurs vestibulaires pourrait être produite soit par diffusion du DFP dans l'endolymphe soit par destruction de l'acétylcholinestérase des fibres vestibulaires efférentes.

Successivement Rossi, Voena, Buongiovanni & Cortesina (1964) ont étudié les effets produits sur la fonction vestibulaire du lapin par l'introduction dans l'endolymphe d'acétylcholine, de composés anticholinergiques (atropine, tétraéthylammonium) et de substances pourvues d'activité anticholinestérasique (diisopropylfluorophosphate).

L'introduction dans l'endolymphe de ces substances a été obtenue par une double fenestration du canal semi-circulaire latéral et l'étude fonctionnelle a été accomplie par enregistrement électronystagmographique.

Tout en tenant compte des réserves d'ordre technique (impossibilité d'établir avec exactitude la quantité de chacune des substances employées qui agit sur le neuroépithélium) et d'ordre pharmacologique (possibilité d'action pharmacodynamique directe ou détermination d'effets *opposés* en rapport à la concentration de quelques-unes des substances employées) *il paraît* possible de déduire, à travers ces expériences, que une accumulation d'acétylcholine au niveau des expansions synaptiques efférents empêche la transmission des impulsions afférentes en agissant sur des structures anatomiques que l'on ne peut exactement identifier mais qui font certainement partie

du système formé par la cellule ciliée et par la fibre nerveuse afférente

Les résultats de ces recherches font en outre supposer que l acétylcholine prenne part au mécanisme de la transmission de l impulsion nerveuse de la cellule ciliée à la fibre afférente

Les résultats obtenus par Rossi Voena Buongiovanni & Cortesina (1964) sembleraient par conséquent démontrer que l acétylcholine *prend part* au niveau du neuroépithélium des crêtes acoustiques au mécanisme qui détermine et règle la transmission des impulsions afférentes

SUMMARY

The efferent innervation of the vestibular receptors is discussed in the light of data of current literature and of personal experimental findings

ZUSAMMENFASSUNG

Der Autor legt die Daten der Literatur dar und erlautert die Ergebnisse von personlichen morphologischen und funktionellen Forschungen über die heraus fuhrenden Nerven des Vorhoforgans

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RHINOPHARYNGEAL CHORDOMA

Report of a Case

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Chordoma is a rare tumour. As it must be borne in mind in the differential diagnosis of intracranial and nasopharyngeal tumours, it seems justified to publish the following case.

CASE HISTORY

A 60-year-old woman (case rec. 45) entered the ENT Department of Sundby Hospital on Apr. 9, 1962. She was a twin, No. 4 of a family of 13. Her twin sister died of consumption at the age of 19.

In early childhood the patient had suffered from middle ear infection and she had gradually become deaf about the age of 14, and had aural discharge at the time. Operation had been contemplated but given up as the patient was "too weak".

At 16 the patient had inflammation of the eyes, so severe that for several months she was blind. She was treated by an ophthalmologist for one year. Her vision gradually returned but was impaired. However, she could move about on her own and read without glasses.

At the age of 27 she had been in hospital for a month with concussion sustained in a traffic accident.

At 31 tuberculosis, 6 months in a sanatorium.

Present complaints

During the past 9 months or so the patient had been troubled periodically by intense headache and also, for about a year, by a greatly reduced passage of air through the left side of the nose. No dizziness, nausea, vomiting, dysphagia, anorexia, diplopia, or other visual disturbances. No complaints from other organ systems.

In March 1962 she had consulted a specialist who had evacuated foul-smelling pus from the maxillary antra on 5 occasions. As the symptoms remained unchanged, she was admitted for further evaluation in April 1962.

The *physical examination* showed a woman of middling nutritional state, impossible to contact except in writing, and even that was difficult.

B.P.: 180/100.

Eyes: Opacities of both corneae.

Right ear: Drum scarred and retracted, but no definite details.

Left ear: Total defect of the drum without visible ossicles. Some serous discharge at the bottom and a somewhat injected promontorial wall.

Hearing 0/0 to shouting. A tuning fork was not heard.

Right and left mastoid regions normal. No facial palsy.

Nasal cavity: Marked septal deviation to the left, the septum being displaced almost to the lateral wall. Some mucous secretion. On the right no abnormality.

The rhinopharynx could not be inspected because of reflexes.

Hypopharynx, larynx: No abnormalities.

Otherwise the physical examination showed no abnormalities.

X-ray investigation of the *nasal sinuses* and of the *skull*, with a particular view to the sellar region, with *tomography* of the sella in the sagittal and frontal plane, as well as *tomography of the nasal sinuses* revealed intense blurring over the maxillary antrum and ethmoid cells on the left. Moreover there was extensive destruction of the sella, the dorsum being absent and the floor of the sella being destroyed. In the sellar region, at the site of the sphenoidal sinus and in the rhinopharynx there were irregular, partially confluent calcific patches in an area measuring 4 × 6 cm in the sagittal plane. In the frontal plane the calcifications also measured 4 × 6 cm. They were situated mainly on the right of the midline. The calcifications were surrounded by a shadow of a soft structure filling the rhinopharynx and extending anteriorly into the choanae and distally to the hard palate. The nasal septum was blurred posteriorly.

X-ray diagnosis: Maxillary and ethmoidal sinusitis. Tumour of the rhinopharynx and base of the skull with calcification (chordoma?). (sd.) Th. Rosendal.

Ophthalmological examination

Vision in right eye 6/24 ÷ 6.50 sph. Vision in left eye 6/60 ÷ 3.00 sph. Moderate paresis of the left lateral rectus muscle. Slit lamp: Deep parenchymal opacities centrally in the cornea, looking like dystrophies. Chamber deep. Iris and pupil normal. Moderate incipient cataract in both eyes. Visual fields to white and red object 10/1000 normal. Ophthalmoscopy: Media clear. Optic disc oval (vertically), pale, with flat excavations, myopic. Moderate vascular sclerosis. No extravasations.

Diagnosis: Excessive myopia. Corneal opacities or dystrophy of both eyes. Paresis of the left abducens nerve. (sd.) Vedel Jensen.

Under intubation anaesthesia she had *direct rhinoscopy and biopsy of a rhinopharyngeal tumour*. The rhinopharynx could not be properly inspected until the soft palate had been mobilized. The tumour completely filled the rhinopharynx. Downwards it was rather nodular, but appeared to be covered by smooth mucous membrane. The mucosa was incised, pulled aside, and two specimens were removed for microscopic study (with a view to possible chordoma).

Histological examination of the biopsy specimens

Small irregular tissue pieces without a surface lining. The tissue was built up of numerous vesicular cells, showing in places ample ground substance



Fig. 1. X-ray of the sellar region showing extensive destruction of the sella. The arrows indicate the calcifications of the tumour.

Nuclei small and uniform, in several places flattened, especially in the vesicular cells. The ground substance and the content of the vesicular cells stained with PAS as well as mucus staining. In some areas there was calcification. No bleeding or necrosis and no signs of malignancy. Three diagnoses were contemplated: Myxomatous fibroma, sialoma and chordoma, but the histological appearances as a whole, especially the vesicular cells, were highly suggestive of chordoma (sd.) H. Hornbak.

The patient was then discharged and referred for out-patient treatment at the Radium Centre. During the next two months she attended there as an out-patient having telecobalt therapy, a total dose of about 5000 r in 46 days. The tumour appeared to remain unchanged, and the patient's complaints of nasal obstruction, dryness of the pharynx, and headache were also unchanged.

During the subsequent 6 months she was followed monthly at the Radium Centre, and her complaints remained the same as stated above. She had furthermore developed severe fatigue, anorexia, and weight loss (about 14 kg in 6 months). Allegedly her visual acuity had not further deteriorated. She could still move about on her own and read without glasses. She could also attend to her job of washing stairs.

At intervals of a couple of months she had three control X-ray investigations of the skull which each time showed completely unchanged appearances. Ten months after her admission to Sundby Hospital the patient died after a traffic accident, being run over by a motor cycle. She got a cranial injury

and injury to the left kidney and succumbed 2 hours after the accident to cerebral oedema and trauma to the left kidney.

Autopsy revealed at the site of the pituitary gland a 3 × 4 cm oval tumour which was asymmetric, larger on the left. The tumour displaced the vessels on the left and the left optic nerve was distinctly reduced in size. A cylindrical piece of tissue comprising the sella turcica and rhinopharynx was sawn off the base of the skull and fixed. It was difficult to judge the appearances and to distinguish the tumour tissue macroscopically from the surrounding normal structures. At any rate there was indubitable invasion of the skeletal tissue at the site of the clivus. The tumour tissue extended down into the rhinopharynx which it filled almost completely. The tumour covered the pharyngeal opening of the Eustachian tubes and covered the choanae almost completely. The tumour tissue was lined with an apparently normal mucosa. No signs of ulcerations. On section there were several calcifications and the cut surface was pale with minor punctate bleedings. Consistency semi-solid. No hard areas.

Microscopic examination

Tumour tissue of highly varying structure, there being areas which were built up of vesicular cells with a small central nucleus and distinct cytoplasmic vacuolization, large areas resembling most of all young cellular and fairly afibrillar connective tissue, several areas which were cartilaginous in nature if anything, areas looking like osteoid tissue, and lastly in a few places a little skeletal tissue, possibly remains of the pre-formed but now destroyed bone. Moreover there were scattered small calcifications and in some of the sections peculiar large necroses looking rather like fibrinoid necroses. There were several vessels in the tumour tissue. Also strands with ample collagenous fibrils. The tumour was characterized especially by the strikingly large areas which looked most of all like young connective tissue. Such areas may be found in chordomas which are untreated, but it is very likely that the characteristic appearance of the tissue was due to the X-ray therapy. The vascular changes and the collagenous tissue might also be radiation reactions. The present tumour contained a strikingly small number of the characteristic vacuolized, so-called physaliphorous cells. However, there was no doubt about the diagnosis: chordoma.

Chordoma was first described by Virchow (1857) who had found these tumours on the clivus Blumenbachii. He called them ecchondrosis physaliphora, assuming that the peculiar cellular formations were due to vacuolar degeneration in cartilage derived from spheno-occipital synchondrosis. Müller (1858) opposed this theory, claiming that the tumours arose from remnants of the notochord, of which they reminded in histological structure. This was verified by Ribbert (1894) who suggested the term chordoma.

Most authors (Binkhorst et al. 1957, Brandstrup 1943, Essamma 1959, Jepsen 1951, Lage Hellmann 1955) have classified chordomas into



Fig. 2. Histologically the tumour consisted of vesicular cells with small and uniform nuclei. In places ample ground substance.

1. Cranial comprising clivus chordoma, pituitary chordoma, naso pharyngeal chordoma and dental chordoma (the latter arising from the epistropheus)
2. Vertebral chordomas and
3. Sacral chordomas

The cranial chordomas which comprise about one third of all these tumours usually arise in the clivus. Up till 1955 only 300 cases were on record (Låge Hellmann 1955).

To give a further impression of the rare occurrence of this type of tumour it may be mentioned that according to Binkhorst *et al.* (1957) only 3 (intra cranial) chordomas were found among 3390 cerebral tumours.

The Danish literature so far contains only 8 cases of cranial chordoma. The first case was described by Fabricius Møller (1919) a rhinopharyngeal chordoma in a boy aged 16. Brandstrup (1943) reported the case of a 73 year old man who was admitted to a neurological department with bulbar paralysis. This case gave rise to great differential diagnostic difficulties. At autopsy the patient was found to be suffering from a clivus chordoma.

Chordoma has also been described within ophthalmology. Møller H. U. (1939) reported on a patient with clivus chordoma whose symptoms were very likely those of glaucoma except for the absence of an increase in intraocular tension. Sorensen (1937) reported two cases, Godtfredsen (1944) one (among

and injury to the left kidney and succumbed 2 hours after the accident to cerebral oedema and trauma to the left kidney.

Autopsy revealed at the site of the pituitary gland a 3 × 4 cm oval tumour which was asymmetric, larger on the left. The *tumour displaced the vessels* on the left and the left optic nerve was distinctly reduced in size. A cylindrical piece of tissue comprising the sella turcica *and rhinopharynx* was sawn off the base of the skull and fixed. It was difficult to judge the appearances and *to distinguish the tumour tissue microscopically from the surrounding normal* structures. At any rate there was indubitable invasion of the skeletal tissue at the site of the clivus. The tumour tissue extended down into the rhinopharynx which it filled almost completely. The tumour covered the pharyngeal *opening of the* Eustachian tubes and covered the choanae almost completely. The tumour tissue was lined with an apparently normal mucosa. No signs of ulcerations. On section there were several calcifications and the cut surface was pale with minor punctate bleedings. Consistency semi-solid. No hard areas.

Microscopic examination

Tumour tissue of highly varying structure, there being areas which were built up of vesicular cells with a small *central nucleus and distinct* cytoplasmic vacuolization, large areas resembling most of all young cellular and fairly afibrillar connective tissue, several areas which were *cartilaginous* in nature, if anything, areas looking like osteoid tissue, and lastly in a few places a little skeletal tissue, possibly remains of the *pre-formed but now* destroyed bone. Moreover there were scattered small calcifications and in some of the sections peculiar large necroses looking rather like fibrinoid necroses. There were several vessels in the tumour tissue. Also strands with ample collagenous fibrils. The tumour was characterized especially by the strikingly large areas which looked most of all like young connective tissue. Such areas may be found in chordomas which are untreated, but it is very likely that the characteristic appearance of the tissue was due to the X-ray therapy. The vascular changes *and the collagenous tissue might also be radiation reactions*. The present tumour contained a strikingly small number of the characteristic vacuolized so-called physaliphorous cells. However, there was no doubt about the diagnosis chordoma.

Chordoma was first described by Virchow *(1857)* who had found these tumours on the clivus Blumenbachii. He called them *ecchondrosis* physaliphora, assuming that the peculiar cellular formations were due to vacuolar degeneration in cartilage derived from spheno-occipital synchondrosis. Müller (1858) opposed this theory, claiming that the tumours arose from remnants of the notochord, of which they reminded in histological structure. This was verified by *Ribbert (1891)* who suggested the term chordoma.

Most authors (*Binkhorst et al.* 1957, Brandstrup 1951, Essamma 1959, Jepsen 1951, Lage Hellmann 1955) have classified chordomas into



Fig 2 Histologically the tumour consisted of vesicular cells with small and uniform nuclei In places ample ground substance

1 Cranial, comprising clivus chordoma pituitary chordoma, naso pharyngeal chordoma, and dental chordoma (the latter arising from the epistropheus)
2 Vertebral chordomas, and
3 Sacral chordomas

The cranial chordomas which comprise about one third of all these tumours usually arise in the clivus Up till 1955 only 300 cases were on record (Låge Hellmann 1955)

To give a further impression of the rare occurrence of this type of tumour, it may be mentioned that according to Binkhorst *et al* (1957) only 3 (intra cranial) chordomas were found among 3390 cerebral tumours

The Danish literature so far contains only 8 cases of cranial chordoma The first case was described by Fabricius Moller (1919) a rhinopharyngeal chordoma in a boy aged 16 Brandstrup (1943) reported the case of a 73 year old man who was admitted to a neurological department with bulbar paralysis This case gave rise to great differential diagnostic difficulties At autopsy the patient was found to be suffering from a clivus chordoma

Chordoma has also been descr[illegible]
(193[illegible]



Fig. 3 Internal surface of the base of the skull Brain removed but tumour *in situ*

500 malignant nasopharyngeal tumours), Jepsen (1951) one, and Mauritzen Christensen & Zachariae (1959) two cases of cranial chordoma

Chordoma occurs with equal frequency in males and females According to Binkhorst it may occur at any age, even be present at birth It is most common about the age of 30 Bourgeois & Franck (1954) have described a case in a 10 year old boy The frequent history of cranial injury has been mentioned by Brandstrup (1943) and Crikelair & MacDonald (1955)

The tumours have ranged in size from pea to orange It is encapsulated and has a smooth surface, of a bluish red colour On section the capsule is usually seen to surround a gelatinous matrix, or else the cut surface may be more motley, having firm homogeneous areas alternating with gelatinous masses *Histologically*, they are characterized by large polygonal, usually vacuolized cells with an eccentric, dark nucleus The cells are situated in clumps or singly Most authors (Essamma, 1959, Labayle & Briand, 1960, Mancoll & Snelling, 1952, Ormerod, 1960) have described the histological appearance as being non malignant

However, Binkhorst (1957) states that histological signs of malignancy

are not uncommon as pronounced aplasia irregular dark nuclei and numerous mitoses are often seen

Its growth is nearly always slow but the tumour is of a malignant nature its growth being invasive and destructive The average survival time from the onset of the first symptom is about 2 3 years

There is some disagreement as to whether the tumour gives rise to metastases According to *Godtfredsen* (1944) metastases have been found in the liver and lungs but not in lymph nodes but Lige Hellmann (1955) and *Ormerod* (1960) have mentioned metastases to the lymph nodes Mancoll & Snelling (1952) state that metastases to the lymph nodes are observed in 11%

The symptoms of course depend upon the localization of the tumour In more than one third of all cases there will be headache and visual disturbances usually diplopia The initial symptoms are very often neuro ophthalmological i e frontal headache restriction of the visual field impaired visual acuity and paresis of the ocular muscles (abducens trochlear and oculomotor paresis) leading to diplopia anisocoria and ptosis The ocular symptoms often appear very suddenly Moreover there may be compression of the trigeminus with trigeminal neuralgia and paresis of the muscles of mastication as well as lesions of the facial and auditory nerves

Compression of the pituitary gland pons and medulla oblongata gives rise to endocrine disturbances pontine and bulbar symptoms Extracranial invasion of the tumour into the orbit maxillary antrum and rhinopharynx may cause exophthalmos pressure pain over the maxillary sinus and the root of the nose discharge of mucopus from the nose epistaxis and nasal obstruction Anosmia and impaired hearing may also occur because of occlusion of the Eustachian tubes

X rays show in advanced stages pronounced skeletal destruction often of the sella turcica Frequently there are calcifications in the tumour

Sorensen (1937) described Sosmann s sign i e a small indentation in the clivus blumenbachii just behind the dorsum sellae Since however this *indentation* is a very early sign and since the tumour is generally in an advanced stage having destroyed the clivus before the patient develops symptoms and seeks medical advice this sign is of little practical value

The treatment is excision to the widest possible extent and palliative X ray therapy

Differential diagnosis In respect to differential diagnosis tumours of the same site must be borne in mind This applies e g to pituitary adenoma craniopharyngioma meningioma acoustic tumour lympho epithelioma reticulo sarcoma and rhinopharyngeal fibroma

The final diagnosis can be made only by biopsy

ZUSAMMENFASSUNG

Oben ist eine Beschreibung von Chordoma rhinopharyngs einer 60jährigen Patientin gegeben Speziell sind die klinischen radiologischen histologischen und differentiell diagnostischen Überlegungen hervorgehoben



Fig. 3. Internal surface of the base of the skull. Brain removed but tumour *in situ*.

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NYSTAGMUS RESPONSES OF THE CAT TO ROTATION AND TO DIRECTIONALLY EQUIVALENT AND NON-EQUIVALENT STIMULI AFTER UNILATERAL CALORIC HABITUATION

William E. Collins
Oklahoma City, Okla., U.S.A.

From the Civil Aeromedical Research Institute, F.A.A., Oklahoma City

Six cats were exposed to mild angular accelerations before and after a series of 15 caloric irrigations. All trials were in total darkness. Slow phase displacement of the eyes, beat frequency and duration of nystagmus were scored. All 3 measures reflected declines in both the primary and the secondary reactions during the course of caloric irrigations. Responses to rotation following the caloric habituation showed almost no change, i.e., there was no apparent stimulus generalization. Some possible causes for the failure to obtain transfer were examined. Additional unilateral caloric trials confirmed reports that the reduction of nystagmus is specific to the direction elicited during habituation trials.

Cats have demonstrated a decline ("habituation") in the nystagmic response to repeated unilateral caloric irrigation in illumination (Henriksson, Fernandez & Kohut 1961, Henriksson, Kohut & Fernandez 1961), to repeated rotation in total darkness (Collins 1963*b*, Crampton 1961, 1962*a*, Crampton & Schwam 1961) and to rotation with concommitant optokinetic stimulation (Crampton 1962*b*). Further, if the elicited nystagmus is limited to a single direction during the habituating trials, there appears to be no transfer of the response decline to vestibularly induced eye movements in the opposite direction (Crampton 1962*a*, Henriksson et al. 1961).

The question of transfer involves stimulus modality as well as directional effects. Working with rabbits, Maxwell, Burke & Reston (1922) and Hood & Pfaltz (1954) reported habituation of rotation-induced nystagmus but normal responses from the unilateral caloric irrigations which followed the rotatory trials. Collins (1963*b*) found little transfer in the cat; the frequency of the beats to caloric stimulation was reduced by about one third after an intervening series of 15 rotations. Dunlap (1925) obtained a marked stimulus transfer by abolishing nystagmus through caloric irrigation of the canals first on one side of the heads of rabbits and then on the other. He obtained no nystagmus to rotational stimuli after these treatments.

The present study was designed to examine, with cats, (*a*) the question of transfer of caloric nystagmus habituation to the rotational situation, (*b*) the manner in which caloric habituation occurs in total darkness, (*c*) the effects of stimulus repetition upon the secondary nystagmus.

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The question of transfer involves stimulus modality as well as directional effects. Working with rabbits, Maxwell, Burke & Reston (1922) and Hood & Pfaltz (1954) reported habituation of rotation-induced nystagmus but normal responses from the unilateral caloric irrigations which followed the rotatory trials. Collins (1963*b*) found little transfer in the cat; the frequency of the beats to caloric stimulation was reduced by about one third after an intervening series of 15 rotations. Dunlap (1925) obtained a marked stimulus transfer by abolishing nystagmus through caloric irrigation of the canals first on one side of the heads of rabbits and then on the other. He obtained no nystagmus to rotational stimuli after these treatments.

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METHODS

Apparatus

Stimulating, restraint and recording equipment were identical to those reported elsewhere (Collins, 1963*b*). The rotatory device described by Guedry & Kalter (1956) was situated in a light-proof room. All testing, including caloric irrigation, was conducted with the animal positioned on the turntable. Restraint was effected according to the technique of Henriksson *et al.* (1961) with positioning accomplished by raising or lowering the animal's head.

The recording device, an Offner Type T Electroencephalograph, employed a 1.4 sec RC time constant in amplification. Needle electrodes were positioned by the outer canthi for the recording of horizontal components of nystagmus. An indifferent electrode was located on the crown near the mid-line of the skull. Signals were led to a terminal box, through slip rings, to the recorder located in an adjoining room.

Procedure

The test room was in total darkness during all trials. The habituation series consisted of 15 consecutive caloric irrigations of the right ear of each animal. Water temperature was kept at 23.5°C (±0.5°C). The tests of transfer (pre- and post-tests) consisted of above-threshold CCW accelerations (4.15°/sec² for 13 sec) and subthreshold decelerations (0.18°/sec² for 333 sec) with the animal's head positioned at the center of rotation. The rotation schedule comprised: (*a*) 30 sec at a constant velocity of 1 rpm, (*b*) acceleration, (*c*) 60 sec at a constant velocity of 10 rpm, (*d*) deceleration to zero velocity. The combination of CCW threshold accelerations and subthreshold decelerations, and irrigation of the right ear with cool water, was designed to limit the elicitation of primary nystagmus to a single direction, viz. with the fast phase to the left. Stimulation always began within 10 sec of the onset of total darkness. Rest intervals of 12-15 minutes separated trials.

Data from 6 of 10 cats are presented here. The four discarded records were due to (*a*) interruption of recording by loss of electrode contact (1 animal), (*b*) responses to the pre-test or to the first irrigation were too poor to be quantified (3 animals). To obtain further data from the same set of 6 animals, additional trials were conducted following the post-test. Two animals each were stimulated with (*a*) warm water (53.5°C) in the untested (left) ear (to elicit nystagmus in the same direction as that occasioned during habituation), (*b*) warm water (53.5°C) in the tested (right) ear, (*c*) cool water (23.5°C) in the untested (left) ear. The latter two conditions each produced nystagmus in the opposite direction from that elicited during the habituation trials. Thus the question of directional transfer could also be examined. A procedural outline appears in Table I.

RESULTS

Measurements of slow phase displacement, frequency and duration of nystagmus were obtained from each animal. Scoring for the primary response

TABLE 1 *The procedural conditions employed*

Cats	Trials	No of trials	Conditions	Last phase direction
All	Pre test	1	4 15°/sec² CCW accel for 13 sec sub threshold decel	Left
All	Habituation	15	23 5°C water to right ear for 30 sec	Left
All	Post test	1	4 15°/sec² CCW accel for 13 sec sub threshold decel	Left
1 and 2	Directional transfer	1	53 5°C water to left ear for 30 sec	Left
3 and 4	Directional transfer	1	53 5°C water to right ear for 30 sec	Right
5 and 6	Directional transfer	1	23 5°C water to left ear for 30 sec	Right

began with the onset of acceleration in the pre and post tests and with the termination of irrigation in the caloric series Secondary nystagmus (a nystagmus which follows and beats in a direction opposite to that of a declining primary response in the apparent absence of physical stimulation) was scored from the point of its onset

Examples of recorded nystagmus responses appear in Fig 1 A clear decline in the vigor of the caloric reaction as a result of repeated elicitation is evident for both of the animals represented The post test acceleration records show only minor changes from the pre test durations for primary responses are somewhat shorter the beats seem more regular and the secondary nystagmus begins somewhat earlier

Slow phase and frequency plots against time were made for caloric trials 1 5 10 and 15 (Fig 2) They indicate that (*a*) a considerable overall reduction has occurred within *the first 5 trials* (*b*) additional stimulation results in a further overall reduction of the response

Total response per trial measures appear in Fig 3 A decline in all aspects of the response (frequency slow phase activity, and duration) is evident for both the caloric and *rotatory data* The decline in caloric reactivity [illegible]

[illegible] slow phase displacement are by factors of about one third

Figs 4 and 5 contain slow *phase displacement* and beat frequency curves obtained by stimulating the right ear with warm water or the left ear with either warm or cool water These trials were conducted after the post test rotations The data clearly indicate that unilateral caloric habituation is specific to the direction *elicited during* habituating trials

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Total response per trial measures appear in Fig 3 A decline in all aspects of the response (frequency slow phase activity and duration) is evident for both the caloric and rotatory data The decline in caloric reactivity is marked although less regular than the function obtained for rotation (Collins 1963*b*) Duration of the rotation induced nystagmus is only slightly reduced and the drops in frequency and in slow phase displacement are by factors of about one third

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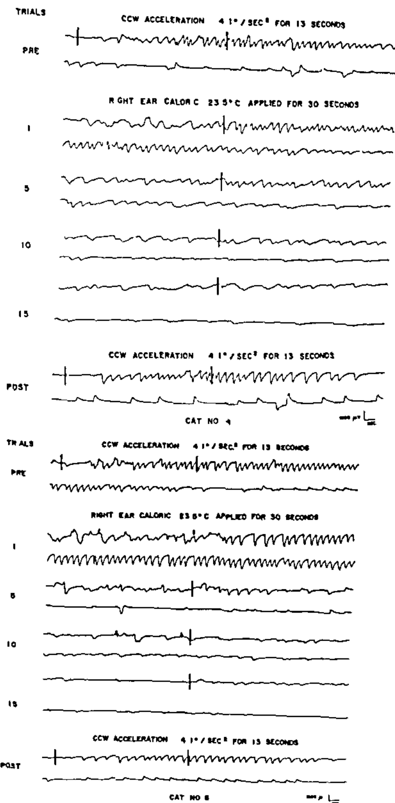


Fig 1 Nystagmus tracings obtained from two cats Pairs of heavy vertical bars demarcate the acceleration periods The single vertical bars through the caloric records indicate the termination of irrigation (tracings include the last 14 sec of irrigation) The decline in caloric reactivity is clearly evident Note the more regular responses to acceleration the drop in frequency and the earlier onset of secondary nystagmus during the post test A secondary reaction is also evidenced in caloric trial 5 for Cat 6

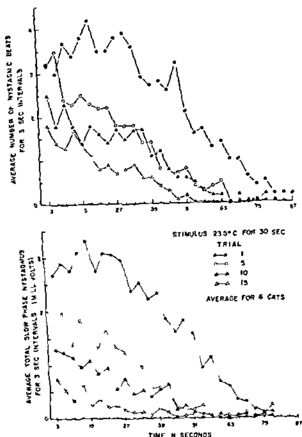


FIG 2 Alterations in the caloric response curve with repeated stimulation Zero time indicates the termination of irrigation A considerable reduction in response occurs within the first 5 trials

condary is extremely irregular in early trials, but shows a definite decline with repeated elicitation (Fig 6) The pre and post test (rotation) secondary shows very little change The one exception is an increase of one fourth to one third in duration of the post test response (Fig 7)

DISCUSSION

Primary nystagmus

Repeated unilateral caloric irrigation of the cat in total darkness results in a marked decline in slow phase displacement, frequency, and duration of vestibular nystagmus These findings are in agreement with caloric data obtained by Henriksson *et al* (1961) under conditions of illumination and with results reported by others (Collins, 1963*b*, Crampton, 1961, 1962*a*, Crampton & Schwam, 1961) for repeated rotational stimulation The greatest amount of decline occurs during the first 5 trials (Fig 3) This closely parallels the manner in which rotation induced primary nystagmus habituates (Collins, 1963*b*).

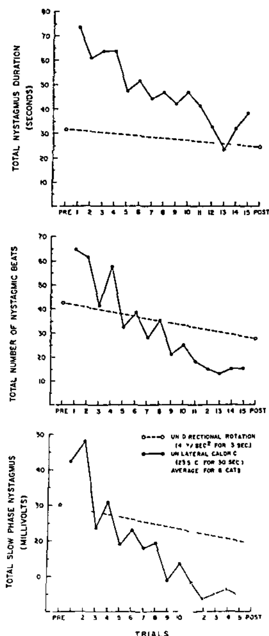


Fig 3 Average slow phase displacement, duration, and frequency of nystagmic beats for the pre and post test responses to angular acceleration and for the 15 caloric trials Pre and post test changes are slight considering the marked drop in the response to caloric stimulation

Transfer of Habituation

Stimulus transfer

The pre and post test rotation data (Fig 3) show a general but small decline effected by the intervening calorizations Of the 3 measures, duration of response is least affected, while the total frequency and the total slow phase displacement are reduced by approximately one third (Fig 3) This amount of decline is exceedingly small considering the marked alteration in response to the 15 caloric trials and is equivalent to what might be obtained as a result of only 3 or 4 consecutive rotations (Collins, 1963*b*)

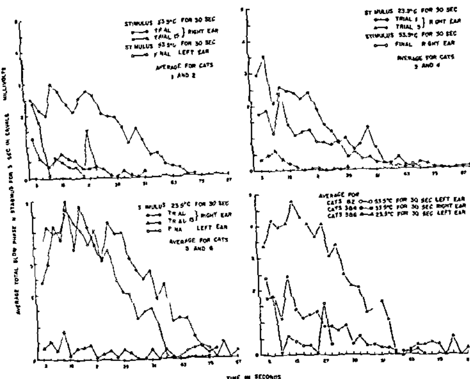


FIG 4 Directional specificity of the caloric response decline in slow phase output A directionally equivalent caloric stimulus applied to the opposite ear, after the series of habituating trials produces a response similar to the last habituation trial (upper left graph Cats 1 and 2) Caloric stimuli which elicit nystagmus in the direction opposite that of the habituation series produce vigorous responses (upper right graph Cats 3 and 4 and lower left graph Cats 5 and 6)

The question of stimulus transfer in vestibular habituation has received little examination Maxwell Burke & Reston (1922) and Hood & Pfaltz (1954) habituated rabbits to rotational stimuli and then found normal responses to caloric irrigation The former however, employed no pre rotation control trial and reported no quantified data while Hood & Pfaltz (1954) based their conclusions primarily upon duration measures More recently Collins (1963b) obtained only minor pre to post test caloric changes from the cat after habituation to rotation It should be noted that in all of these cases there were apparently considerable differences in the intensities of the habituating and transfer stimuli

Dunlap (1925) employed conditions somewhat more similar to those reported here Working with rabbits he completely abolished nystagmus to unilateral ice water caloric irrigation first to one ear, and then the other After this extensive habituation responses to rotation were absent

It has been suggested that differences in the relative intensity of rotatory vs caloric stimulation might have been one cause for the failure to obtain

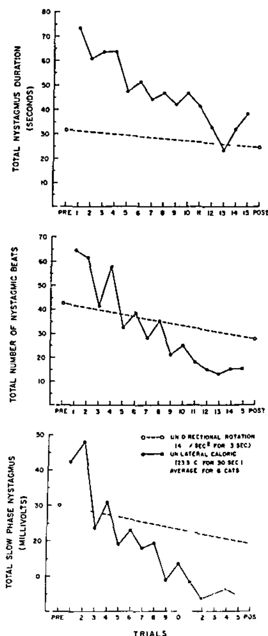


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Stimulus transfer

The pre and post test rotation data (Fig 3) show a general, but small decline effected by the intervening calorizations Of the 3 measures, duration of response is least affected, while the total frequency and the total slow-phase displacement are reduced by approximately one third (Fig 3) This amount of decline is exceedingly small considering the marked alteration in response to the 15 caloric trials and is equivalent to what might be obtained as a result of only 3 or 4 consecutive rotations (Collins, 1963*b*)

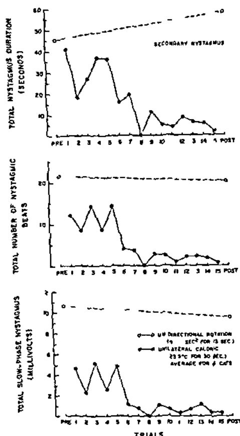


Fig 6 Average slow phase displacement, duration and frequency of secondary nystagmus obtained during successive trials A decline in all aspects of the caloric secondary is evident although animals were not consistent in yielding such responses All animals demonstrated a secondary to the pre and post test accelerations

the other stimulus condition, to change not only the neural pattern, but the plane of the response as well

Response transfer

Henriksson *et al* (1961) have presented data which show that unilateral caloric nystagmus habituation is specific to the direction of the response elicited during the habituating trials Data obtained in this study (Figs 4 and 5) provide confirmation of their findings Thus, after a specific direction of nystagmus has been habituated by repeated unilateral irrigations, a stimulus applied to the opposite ear, which drives the response in the same direction as that of the habituating trials shows a marked depression of reaction On the other hand, stimuli applied unilaterally to either ear, which provoke a response in the direction opposite that of the habituating trials, result in a vigorous nystagmus Crampton (1962*a*) has presented data which

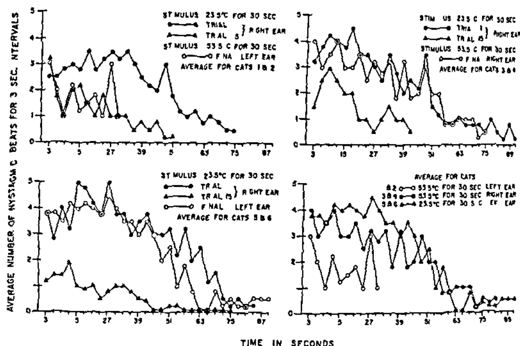


Fig. 5. Directional specificity of the caloric response: decline in frequency of nystagmus. The data are highly similar to the results presented for slow phase activity.

transfer of habituation from rotation to the caloric situation (Collins 1963*b*). The importance of this intensity variable for differences within a stimulus modality has been noted (Griffith 1920, Guedry 1953, Maxwell, Burke & Reston 1922) but has not received intensive investigation. It appears that after habituation to a given level of stimulation, a more intense stimulus may evoke a brisk response.

A second factor has also been suggested to account for the failure to obtain positive results in transfer tests (Collins 1963*b*). Data obtained here lend some support to its possible importance. In the present study the initial caloric nystagmus output exceeded the rotation response by a considerable amount. Thus the animals were habituated to a stimulus which was initially more intense than that experienced during the pre- and post-tests. This intensity difference would appear to favor a transfer effect. That such transfer did not occur might be accounted for by differences in the neural excitation patterns generated by unilateral and bilateral stimulation. That is, the habituating mechanism may respond with a relative specificity that is related to whether a single horizontal semicircular canal is stimulated repetitively or whether both canals are simultaneously activated.

The two explanatory factors outlined above are not, of course, mutually exclusive. Further, the pattern of neural activity produced by the caloric irrigation (which effected a cooling of the entire labyrinth) may have differed enough from that produced by rotation to result in habituation specific to the caloric stimulus. In addition, inaccuracies in positioning of the animal's head might elicit sufficient stimulation of the vertical canals under one or

difference may be due to more sustained high levels of arousal in man (Collins & Poe 1962, Crampton 1961, Crampton & Schwam 1961) or to the selection of the human subjects.

In the present study, no consistent relationship between primary and secondary output to the caloric stimulation can be readily expressed. That the secondary declines is clear. The decline, however, is abrupt after trial 5 (Fig. 6) and quite irregular. During the first 5 trials, secondary nystagmus alternately declines markedly and returns to its initial level.

All of the animals gave secondary responses to the pre- and post-test rotation trials and to the first caloric irrigation. Thereafter, however, the number of cats producing secondary responses varied from 1 to 5 for trials 2 through 7, no secondary responses were recorded during trial 8—and similarly from 1 to 5 for trials 9 through 15. Its appearance in a given animal is thus not consistent.

No striking overall change in slow phase displacement or frequency occurred in the pre- to post-test comparisons of secondary nystagmus. Duration of the response increased, however, during the post-test (Fig. 7). Parenthetically, it might be added that the tests employing equivalent (53.5°C to the left ear) and non-equivalent (53.5°C to the right ear and 23.5°C to the left ear) stimuli showed only a few scattered beats of secondary responses.

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Data collected with the technical assistance of Kenneth L. Swain while the author was at the U.S. Army Medical Research Laboratory, Fort Knox, Ky. The assistance of Joseph L. Duchon and Mary Jayne Capps in the process of data reduction is gratefully acknowledged.

ZUSAMMENFASSUNG

Sechs Katzen wurden vor und nach fünfzehn kalorischen Ohrspülungen leichten angularen Beschleunigungen ausgesetzt. Alle Versuche wurden in vollkommener Dunkelheit vorgenommen. Die Phase der langsamen Augenbewegung, die Frequenz und Dauer des Nystagmus wurden aufgezeichnet. Alle drei Messungen wiesen eine Abschwächung in der primären und sekundären Reaktion während der Ohrspülungen auf. Die nachfolgende angulare Beschleunigung zeigte keine besonderen Änderungen. Mögliche Ursachen dafür wurden untersucht. Zusätzliche unilaterale kalorische Versuche bestätigten Berichte, dass die Abschwächung des Nystagmus spezifisch ist für die Richtung, die während der vorausgehenden Ohrspülungen erzielt wurde.

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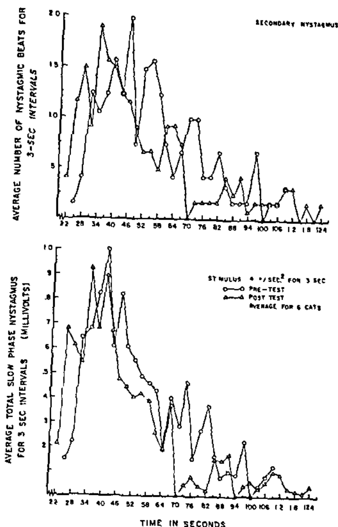


Fig 7 Secondary nystagmus responses to acceleration plotted in 3 sec intervals according to actual time (zero time represents point at which the 13 sec acceleration was initiated) No significant pre to post test changes are evident

indicate a similar directional specificity of cat nystagmus habituated by rotation and Aschan (1954) has noted a relationship between directional preponderance of nystagmus in fighter pilots and their choice of direction in "rolling" their aircraft

Secondary nystagmus

Only a few studies have been concerned with characteristics of secondary nystagmus (e g Aschan & Bergstedt, 1954, Collins, 1962, 1963*a*, *b*, Collins & Poe, 1962, Fluur & Mendel, 1962, Hauty & Wendt, 1960) In the cat, the secondary reaction to rotation has been reported to rise peak, decline, and habituate in a manner highly similar to the primary response (Collins, 1963*b*) In addition, the slow phase rotation-induced output of secondary activity in the cat appears to be about one-fourth to one fifth that of the primary (Collins, 1963*b*), for man, the factor was reported to be about one-half for 3 selected subjects (Hauty & Wendt, 1960) Some of this inter-species

difference may be due to more sustained high levels of arousal in man (Collins & Poe 1962 Crampton 1961 Crampton & Schwam 1961) or to the selection of the human subjects

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SIMPLE MASTOIDECTOMY WITH AIR CHAMBER CREATION IN PROGRESSIVE ADHESIVE OTITIS

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The writer treated 87 ears in the progressive stage of adhesive otitis with simple mastoidectomy and air chamber creation The idea was first to cure the latent mastoiditis present at this stage of the disease and *second to* create a large air space connected with the tympanum During the operation performed via the postauricular approach the granulations with their secretion producing glandlike areas and all soft bone and fluid were removed The final result was an operative cavity with smooth hard walls The *aditus ad antrum* was enlarged slightly to create a communication between the operative cavity and the tympanum The large air filled cavity connected with the middle ear facilitates the functioning of the eustachian tube Pure tone audiograms taken preoperatively and an average of 8 3 months after the operation reveal that both the air and the *bone conduction curves had in most cases* improved The values are calculated as averages for 500 *1000 and 2000* cps No improvement in hearing was achieved by this operation alone at the terminal stage of the disease The etiology *and pathogenesis* of adhesive otitis are discussed

Adhesive otitis presents otologists—at least those of Northern Europe—with considerable difficulties *Problems* of the disease were described by Surala at the 1961 Congress *of* the Scandinavian Oto Laryngological Society, and at the following *Congress* in *1963* the disease was *one of the* main subjects discussed with reports *presented* by Surala Ingelstedt Elsberg Paulsen Bentzen & Palling Iwertsen Grahne Barr & Klockhoff Buch & Kristensen Palva and Arnvig

Surala (1961 1964) distinguishes *three* phases in the course of adhesive otitis In the first *phase the functioning* of the eustachian tube is poor and fluid occurs in the middle ear The second phase is marked by the formation of adhesions and an abacterial latent mastoiditis In the third the terminal phase inflammation is *no longer present* and the ossicular chain is fixed by adhesions

If the disease has led to definitive *scarring* and fixation of the tympanic membrane the windows and the ossicular chain the therapeutical chances of making a permanent *improvement* in hearing are very slight For *positive* results therapy must be *started* at the earliest possible stage

Pathogenesis

It is very likely that the condition arises from poor functioning of the eustachian tube, gradually resulting in permanent tubal occlusion. The tube no longer opens physiologically on swallowing and the middle ear with its air cell system now becomes an enclosed space. Air is absorbed through the mucosal blood vessels until an equilibrium is reached between the partial pressures of air gases in the middle ear and in the blood. The greater the underpressure in the middle ear, the more difficult it is for the tube to open and a vicious circle is established. The partial pressure of air gases in the blood amounts to some 950 cm/H_2O, while the atmospheric pressure equals about 1000 cm/H_2O. Theoretically, therefore, the maximum underpressure in the middle ear should amount to about 50 cm/H_2O, a figure found to comply with measured values (van Dishoeck 1941). The clinical picture of serous otitis opens with mild infection (van Dishoeck 1941, Carpenter 1949, Robison & Nicholas 1951, Grahne 1964). The middle ear and the air spaces of the mastoid process are filled with a fluid which often thickens gradually as a result of diffusion. Since there is no possibility of fluid outflow, the body tries to remove the fluid by organization, a process which some authors consider to be linked with the occurrence of fibrin in the fluid (Kranz 1926, Lange 1928, Singer 1932).

The epithelial lining of the tympanum is largely composed of simple nonciliated cuboidal cells. As the mucosa extends posteriorly to the aditus ad antrum, the antrum and the mastoid air cells, the cuboidal epithelium is gradually transformed into simple squamous, and the mucosa becomes extremely thin and endothelium-like. The fluid and the mild infection irritate the mucosa, and the process of organization begins first in places where the epithelium is lowest, i.e. *in the air cells and the antrum.* The histological developments have been described in detail by many authors (Gorke 1905, Doderlein 1920, Kranz 1924, 1926, Lange 1928, Singer 1932, Ojala 1953). A tiny bud of fibroblastic tissue like the point of a needle grows from the subepithelial connective tissue. This tissue bud emerges through an apparently intact epithelium (Lange 1928), the cells of which give way. New tissue buds shoot up and join to form bridges of tissue. Each bud contains a small gradually growing blood vessel. Initially this blood vessel is solid but a definite lumen soon develops. The blood vessel can occasionally be seen to have developed from a mucosal blood vessel (Doderlein 1920). The pavement epithelium in the vicinity of the bud grows higher, passing rapidly across the newly formed tissue bridges; the organization process has scarcely got under way before the tissue bridge is covered with epithelium. In this way the air spaces of the mastoid process become more or less filled with granulation tissue. Clinically, the changes correspond to those of a latent mastoiditis, and at this stage a mastoidectomy often arrests the disease (Siirala 1960, 1961, Palva 1962, Grahne 1964). Gradually, however, the condition, if not treated, provokes organization processes in the tympanum

though the tympanic mucosa because of its structure and thickness, is more resistant to the process of organization so that the process here often starts at a later stage

Bacteria cannot usually be demonstrated in the fluid or in the granulations in adhesive otitis Many authors have however found bacteria in the preliminary stage of the disease (Forschner 1925 Blegvad 1931, Senturia Gessert Carr & Bauman 1958 Grahne 1964)

The Object of Operative Treatment

An attempt has now been made to study the effect of simple mastoidectomy with the creation of an air chamber, on the progressive stage of adhesive otitis The intention was partly to cure the latent mastoiditis and partly to create a large air space in the mastoidectomy cavity to form a connection between it and the tympanum The mastoidectomy cavity would gradually be lined with a thin mucosa of relatively few blood vessels, and the ratio of the quantity of air in the middle ear to the mucosal surface would be considerably higher than preoperatively The diffusion of air into the blood would be slower The result would thus be a relief in the functioning of the eustachian tube (Flisberg Ingelstedt & Ortegren 1963 Grahne, 1964)

Preoperative Considerations

During the progressive stage of adhesive otitis the deterioration in hearing is often not completely constant Patients frequently complain of impaired hearing in conjunction with common colds Otoscopy at such a time usually reveals a slight redness of the tympanic membrane often most conspicuous in the posterior and posterior superior parts of the membrane These patients often also mention a feeling of heaviness in the ear and sometimes slight pain

The Series

In all the patients of the present series there were evident changes in the tympanic membrane The membrane was mostly thickened cicatrized and retracted and its mobility tested by Siegle s pneumatic otoscope was markedly reduced in every patient Tubal function was unsatisfactory a few patients were able to open the tube by Valsalva inflation no one by Toynbee manoeuvre Exact measurement of the function of the eustachian tube is not possible for such patients with granulations and fluid in the middle ear and the air spaces of the mastoid process

Many of the patients reported a sporadic ear discharge over a number of years but no one reported such discharge from the ear in question during the few months prior to the operation here described All the pathological conditions in the nose and accessory sinuses and in the nasopharynx and pharynx which might adversely affect tubal function had been corrected before the



Fig 1 Specimens fr m antrum showing yo ng granulation tissue with chole terol clefts gla ll ke areas conte l with atrop hic epithelium Inflammation cells Symptoms of a lhesive otitis l l been present for 1 years Mag ×1_0

operation Roentgenograms of the ears to be surgically treated showed without exception a sclerotic mastoid process with few or no air filled cells In no case was the tympanic membrane ruptured All the operations and follow up examinations were performed by the writer in person

The series consisted of 65 patients 40 women and 2› men with the fol lowing age distribution

Years	*No*	*Years*	*No*
0 10	8	41 50	13
11 20	12	51 60	5
21 30	)	61 70	2
31 40	1(		

The total number of ears operated on was 87 since 22 patients had *both* ears treated In additi n an operation was performed on both ears of three small children but these are excluded from the present series because the audiometric technique employed was not in their cases applicable 43



Fig 2 Specimen of granulation tissue from antrum, of varying firmness but more cicatrized and adult than that of Fig 1 because of a 25 year history Numerous cholesterol clefts Mag × 120

ients had the operation performed on one ear only for these the *contralateral* ears showed the following characteristics

1 14 ears had been operated on for cholesteatoma,
2 in 13, there was chronic suppuration of a non cholesteatomatous nature This had in some cases been surgically treated previously,
3 two ears showed adhesive otitis in the terminal stage
4 in seven patients there were slight symptoms of adhesive otitis but the ear had not been operated on
5 in seven patients the ear was healthy with normal hearing

Only these last seven patients who underwent the unilateral operation had therefore a completely healthy contralateral ear The seven patients who showed slight symptoms of adhesive otitis in the non operated ear belonged to the youngest two age groups

Surgical technique was as follows under local (for children general) anaesthesia a simple mastoidectomy was performed via the postauricular approach The fluid and all granulations in the antrum, aditus ad antrum and air cells were removed The aditus ad antrum was widened slightly to ensure good communication with the tympanum All soft bone was removed,

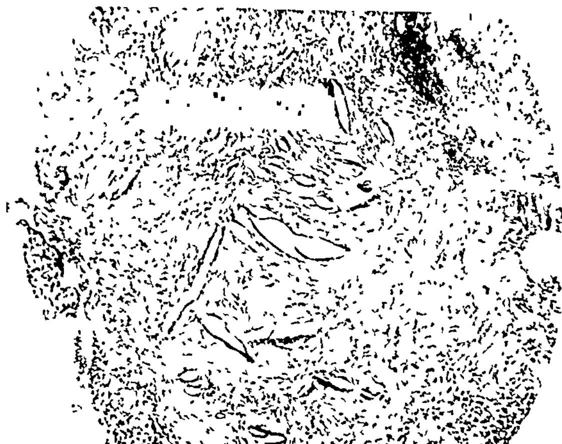


Fig 1 Specimens from antrum showing young granulation tissue with cholesterol clefts glandlike areas coated with atrophic epithelium inflammation cells Symptoms of adhesive otitis had been present for 4 years Mag × 120

operation Roentgenograms of the ears to be surgically treated showed without exception, a sclerotic mastoid process with few or no air filled cells. In no case was the tympanic membrane ruptured All the operations and follow up examinations were performed by the writer in person

The series consisted of 65 patients, 40 women and 25 men, with the following age distribution

Years	No	Years	No
0 10	8	41 50	13
11 20	12	51 60	5
21 30	9	61 70	2
31 40	16		

The total number of ears operated on was 87 since 22 patients had both ears treated In addition an operation was performed on both ears of three small children, but these are excluded from the present series because the audiometric technique employed was not in their cases applicable 43 pat

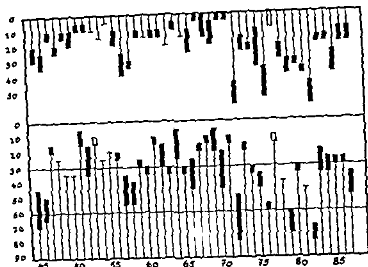


Fig. 4. Audiometer recordings on the remaining 43 ears operated on. The total series consisted of 87 ears (Fig. 3 and Fig. 4).

DISCUSSION

Improvement of hearing was obtained by simple mastoidectomy with air chamber creation in most cases of adhesive otitis provided the operation was performed before the disease had entered its terminal phase. An improvement of bone conduction hearing was also achieved for the majority of cases. These results are apparently attributable to the fact that the operation has a favourable effect on the tympanic mucosa, in which the swelling is reduced and the window niches are opened. Tympanic changes and the inadequate functioning of the eustachian tube usually, however, prevent the hearing from becoming normal.

The writer also performed the operation on many cases in which the disease had reached its terminal stage. The operative finding was eburnation of the mastoid process with an empty antrum and aditus ad antrum lined with a thin, pale mucosa. In these cases the conditions of irritation, i.e. fluid and mild infection, had disappeared, resulting in a definitive cicatrization of the middle ear, and no improvement of hearing was obtained by mastoidectomy and air chamber creation.

In a number of cases not included either in the present series the writer has performed tympanotomy prior to mastoidectomy in order to observe the changes in the tympanum and if possible to try to correct them. Tympanotomy often reveals that the mucosa is so swollen as apparently to fill the window niches. In general the changes in the tympanum are less marked than in the air spaces of the mastoid process, though even small changes in the tympanum may be of the utmost importance to hearing. As pointed out

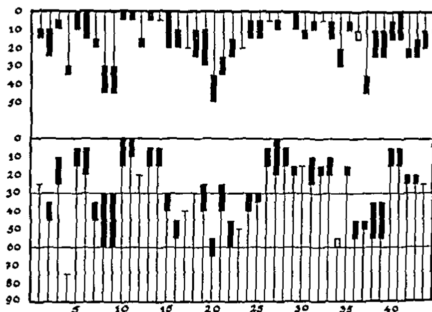


Fig 3 Pure tone audiometer recordings on 44 of the ears operated on Bone conduction shown in the upper part of the figure and air conduction in the lower part The values are quoted as averages of 500, 1000 and 2000 cps The hearing gains are indicated in black columns hearing losses in white columns Recordings were made just before the operation and about 8 months postoperatively

and the final result was an operative cavity with smooth, hard walls The periosteum, the subcutis and the skin were sutured exactly over the operative cavity A thin polyethylene drain, with one end in the operative cavity and the other protruding from the lower part of the incision, was left in place for eight days after the operation The patients remained in hospital for nine days, or if both ears had been operated on, for eleven days Where both ears were operated on an interval of two days was allowed to elapse between the operation on each ear Eustachian tube inflations were not attempted either during or after hospitalization

Histological study of the specimens taken on operation showed a granulation tissue more or less scar like, depending on how long the organization process had been under way There were in addition inflammation cells, cholesterol clefts and secretory areas (Fig 1 and Fig 2)

Follow up examinations were performed one month, three months and eight months postoperatively Patients usually reported that several subjective symptoms had improved the head felt less weighty tinnitus had diminished or ceased, and the feeling of heaviness in the auricular region was less marked Common colds affected the hearing less than before and most patients found that their hearing had in general improved, a fact which could be verified by audiometric examinations Fig 3 and Fig 4 show the state of hearing according to pure tone audiograms taken an average of 8 3 months postoperatively, as compared with those taken preoperatively Changes in both air and bone conduction were recorded as averages for 500, 1000 and 2000 cps

1 As pointed out above several authors have demonstrated bacteria in the initial stages of the disease

2 The clinical finding on mastoidectomy is often the same macroscopically, as in chronic suppurative non cholesteatomatous otitis media

3 Microscopic study of the granulations reveals changes suggestive of a mild infection

4 The patient s medical history often mentions discharge from the ears a finding also recorded by Lumio (1951)

5 If the condition is unilateral there is frequently simultaneous discharge from the other ear

6 In common colds there is often a slight redness in the posterior and superior parts of the tympanic membrane indicating that the granulation tissue of the middle ear reacts inflammatorily The patient s hearing is often temporarily reduced in conjunction with such infections

7 Adenoidal hyperplasia rhinitis and sinusitis are frequently present in these patients i e infections in regions which are developmentally close to one another

Why is it that bacteria can rarely be shown in an ear affected by progressive adhesive otitis? The explanation is perhaps that the condition involves bacteria that have lived in the nasopharynx in a weakened state for a long time before reaching the ear The vitality and virulence of these bacteria is so low that they no longer grow when cultured It is an established fact that samples taken from other distinctly bacterial conditions in the middle ear show surprisingly often no growth on culture (Leutert 1899 Scheibe 1904 Gorke 1905 Schwartze & Grunert 1905 Rosenwasser & Adelman 1957 Goodhill 1958) Fleming (1922) has demonstrated a substance which he calls lysozyme present in the tissues and secretions which is capable of rapidly dissolving certain bacteria Surala & Lahikainen (1952) and Surala & Vuori (1954) have shown that the exudate in acute otitis has a bacteriostatic effect It may be presumed that the fluid in adhesive otitis has a similar effect which moreover on account of the chronic nature of the condition has long been active in the ear

There is hardly any inflammatory disease of the middle ear restricted solely to one part of the middle ear or to the air spaces of the mastoid process pathological changes occur to a greater or lesser degree in all the cavities (Bezold 1902 Lange 1928 Singer 1932 Ojala 1953) The intensity of the inflammatory process in one or other section of the middle ear and its air spaces is however decisive in the appraisal of the clinical picture In the early stages of adhesive otitis the greatest changes are seen in the air spaces of th

osa there is very thin and

the disease now assumes

... mastoiditis Organization phenomena with fresh formation of bone substance finally result in a more or less complete sclerosing of the mastoid process and by the time the disease has reached this stage the changes in the tympanum have caused a marked reduction in hearing It is therefore extremely important to begin therapy in adhesive otitis as

above the mucosa of the tympanum is considerably thicker than that of the air spaces of the mastoid process It offers therefore a considerably greater resistance to irritation by fluid and mild infection All the mucosal layers increase in thickness and this positive defence reaction prevents the process from spreading to the underlying bone In suppurative middle ear infections too this proliferation of the mucosa is decisive and only in exceptional circumstances does the infection spread to bone tissue A bone process in the thin wall of bone separating the middle ear from the inner ear would imply that infection could reach the inner ear In addition to swollen mucosa one often sees organization processes in the form of string like synechiae between mucosal surfaces lying close to each other The sites most favoured are the two window niches the spaces between the auditory ossicles and their connecting bands and the tympanic membrane The tympanic mucosa is covered by low pavement epithelium on the sites exposed to constant vibrations such as the inner surface of the tympanic membrane and the auditory ossicles This low epithelium easily becomes the starting point for organization processes in the tympanum The mucosal surfaces in these narrow passages are close to each other a fact which furthers the formation of tissue bridges Moreover the fluid in these narrow passages is relatively stationary since it is not much affected by the movements of the body—another factor which favours an incipient organization process The cubical epithelium and ciliated epithelium on the other hand are highly refractory For this reason organization processes are seldom seen e g in the neighbourhood of the tympanal opening of the eustachian tube where the epithelium is highest In cases in which organization processes have nevertheless occurred in areas with normally high epithelium Goerke (1905) was able to demonstrate that the epithelium had in fact been lowered as a result of metaplasia

Synechiae to Shrapnell's membrane are frequent Once adhesive otitis has reached its terminal stage with resulting cicatrization Shrapnell's membrane is drawn into the epitympanum At this stage the pars tensa is also retracted The long process of the malleus is drawn inward pushing the short process outward thus increasing tension on Shrapnell's membrane Jordan (1963) is of the opinion that the membrane may even be ruptured as a result Even if this does not occur this deep skin lined pouch in the attic becomes *filled with accumulated layers of cornified epidermoid cells There* thus develops a cholesteatomatous plug which continues to grow exerting pressure against Shrapnell's membrane until the latter is finally ruptured The way is now open *for the cholesteatoma to spread into the middle ear* Such a mechanism for the development of cholesteatoma is also suggested by the relatively high incidence of cholesteatoma in the contralateral ears of those patients *in the* present series who underwent a unilateral operation

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early as possible (Siirala, 1960, 1964; Palva, 1962) Results will be best if treatment can be started when the disease still appears in the form of serous otitis (Armstrong, 1954, 1957; Barr & Klockhoff, 1964; Grahne, 1964)

The present study shows that simple mastoidectomy with air chamber creation may have a favourable effect on adhesive otitis at the progressive stage. It is naturally difficult to say with any certainty how permanent the improvement in hearing will be. It depends very much on whether tubal function will continue indefinitely. In the cases longest observed there has so far been no special tendency to impairment of hearing

Siirala (1960, 1963, 1964) and Palva (1964) have described methods of reconstructing by tympanotomy a functioning air-filled tympanum In many cases not included in the present series tympanotomy was performed shortly after mastoidectomy and air chamber creation During tympanotomy an attempt was made to remove the granulations at least in the region of the window niches, hypotympanum and tubal opening An improvement of hearing beyond that obtained by the previous bone operation was achieved in individual cases The present writer wishes to emphasize the importance of tympanotomy's being preceded by simple mastoidectomy with air chamber creation By this means the latent mastoiditis is cured, secretion-producing granulations are removed, and a large air space is created, all factors ensuring the eustachian tube an improved chance of ventilating the middle ear

ZUSAMMENFASSUNG

Der Verfasser hat 87 Ohren im progressiven Stadium der adhäsiven Otitis durch Antrotomie mit Herstellung eines Luftraumes behandelt Hierdurch sollte zunächst die latente Mastoiditis saniert werden, die in diesem Stadium der Krankheit vorkommt, und zum anderen war das Ziel die Schaffung eines grossen Luftraums in Verbindung mit dem Tympanum Bei der Operation, die auf retroaurikulärem Wege durchgeführt wurde, wurden die Granulationen mit ihren sezernierenden, drusenähnlichen Gebilden, alle weichen und morschen Knochenpartien sowie das Sekret entfernt Das Endresultat war eine Operationshöhle mit glatten, harten Wänden Der Aditus ad antrum wurde etwas vergrössert, so dass die Operationshöhle eine weite Kommunikation mit dem Tympanum bekam Diese grosse, luftgefüllte Höhle in Verbindung mit dem Tympanum bedeutet eine Entlastung der Funktion der Tuba Eustachii Die tonaudiometrischen Untersuchungen, die präoperativ sowie ca 8,3 Monate postoperativ durchgeführt wurden, haben ergeben, dass sowohl die Luft wie auch die Knochenleitungskurve in den meisten Fällen besser geworden war Die Werte wurden als Mittelwerte für 500, 1000 und 2000 Hz berechnet Eine Verbesserung des Gehörs hat der Verfasser mit bloss dieser Operation im Terminalstadium der Krankheit nicht erzielt Die Ätiologie und Pathogenese der adhäsiven Otitis werden diskutiert

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THE REACTION OF GLUCOSE OXIDASE TEST PAPER IN NORMAL NASAL SECRETION

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The reactions of glucose oxidase test paper (Clinistix® and Tes Tape®) were studied in the nasal secretion of 100 nurses Clinistix® gave positive reaction in 75 % and Tes Tape® in 45 % in cases with normal nasal secretion The tests are of limited value in the diagnosis of cerebrospinal rhinorrhoe

A difficult problem in purulent meningitis is the possible presence of a craniopharyngeal fistula in patients with previous head injuries The meningitis may supervene many years after the injury (Frenckner & Richtner, 1960 Boe & Huseklepp 1960) Roentgenological signs of fracture are often lacking

Cerebrospinal rhinorrhoe is a pathognomonic sign of a dura lesion but vasomotor rhinitis may give similar symptoms Identification of the discharge has among other criteria been based upon the demonstration of glucose cerebrospinal fluid contains glucose whereas nasal secretion is supposed not to do so (Lewin 1954) Application of glucose oxidase test paper Clinistix® or Tes Tape® in the nasal cavity therefore should be a convenient way of demonstrating cerebrospinal glucose in normal nasal secretion (Quist Hanssen 1961)

The following investigation was carried out to elucidate this question

In 100 normal nurses without previous head injuries Clinistix® was put in the left nasal cavity and Tes Tape® in the right for about 5 seconds If the paper was dry the procedure was repeated The lacrymal secretion was tested simultaneously with Clinistix® Finally a strip of blotting paper of the same size as *Clinistix®* was put in one of the nostrils and tested with benzidine reagent

Clinistix® gave positive reactions in 75 % and Tes Tape® in 45 % of cases with normal nasal *secretion Half* of the positive reactions were registered as trace According to Ridley (1930) tears contain 0 65 % sugar, which may be responsible for the positive reaction on glucose oxidase test paper In the present study however *Clinistix®* gave positive reaction on lacrymal secretion in 26 % of the cases *and most of these* reactions were faint

A paper induced traumatic lesion of the nasal mucosa might give a positive reaction because of the glucose contents of extravasated blood Though visible blood was not observed on the papers benzidine gave *more or less*

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A difficult problem in purulent meningitis is the possible presence of a craniopharyngeal fistula in patients with previous head injuries. The meningitis may supervene many years after the injury (Frenckner & Richtner 1960, Boe & Huseklepp 1960). Roentgenological signs of fracture are often lacking.

Cerebrospinal rhinorrhoe is a pathognomonic sign of a dura lesion but vasomotor rhinitis may give similar symptoms. Identification of the discharge has among other criteria been based upon the demonstration of glucose; cerebrospinal fluid contains glucose, whereas nasal secretion is supposed not to do so (Lewin 1954). Application of glucose oxidase test paper (Clinistix® or Tes Tape®) in the nasal cavity therefore should be a convenient way of demonstrating cerebrospinal glucose in normal nasal secretion (Quist Hanssen 1961).

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Clinistix® gave positive reactions in 75% and Tes Tape® in 45% of cases with normal nasal secretion. Half of the positive reactions were registered as trace. According to Ridley (1930) tears contain 0.65% sugar which may be responsible for the positive reaction on glucose oxidase test paper. In the present study, however, Clinistix® gave positive reaction on lacrymal secretion in 26% of the cases and most of these reactions were faint.

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Blumsohn & Jackson (1962) demonstrated that moistened glucose oxidase test paper (Tes-Tape®), held between washed fingers gave positive reactions in about 50 %. The same type of reaction may occur in the nose as a consequence of enzymatic activity.

Consequently glucose-oxidase test paper is of limited value in the diagnosis of cerebrospinal rhinorrhoe.

RÉSUMÉ

On a examiné la réaction de la secrétion nasale de 100 infirmières à l'aide du papier test à la glucose-oxidase On a obtenu 75 % de réactions positives au Clinistix® et 45 % au Tes-Tape® chez les personnes examinées ayant une secrétion nasale normale La valeur de ces épreuves, appliquées au diagnostique des rhinorrhee cérébrospinales est très limitée

ZUSAMMENFASSUNG

Die Reaktionen mit Glucose-Oxidase Test papier (Clinistix® und Tes Tape®) wurden im Nasensekret von 100 Krankenschwestern untersucht Clinistix® gab positive Reaktionen in 75 %, Tes Tape® in 45 % bei Untersuchungspersonen mit normaler Nasensekretion Die Proben sind von beschränktem Werte in der Diagnostik des cerebrospinalen Rhinorrhoes

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ENZYME THERAPY IN THE TREATMENT OF SINUSITIS

Streptokinase Streptodornase (Varidase) Buccal Tablets used in the treatment of Sinusitis Maxillaris

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Sixty-one patients with clinically verified sinusitis maxillaris were divided by the date of birth into a treatment group of 31 and a control group of 30 patients.

The treatment group was given as the only difference from the control group 4 Varidase buccal tablets daily. Both groups were treated with penicillin together with sinus puncture and drainage a.m. Proetz on alternate days.

As a criterion for the effectiveness of the treatment the time when a clear irrigation water was obtained on sinus puncture was used.

In the present limited patient material it was found that the Varidase treated group showed a smaller average number of punctures and fewer operated patients than in the comparative control group.

Varidase which is an enzymatic drug (streptokinase streptodornase) obtained from non pathogene strains of haemolytic streptococcus (Lancefield's group C) has been used in the treatment of inflammatory (Golden *et al.* 1958) surgical conditions (Golden & Musgrave 1954) where use has been made of its ability to debride superficial lesions with devitalised tissue and its ability to cause lyses of localized pus and blood clots (Armstrong & White 1950, Tillett *et al.* 1948, Tillett 1950, 1957).

Varidase appears to be an activator of the organism's fibrinolytic system in which the plasminogen is transformed to the fibrinolytic plasmin which hastens the debridement of necrotic tissue, purulent exudate and haematomas (Astrup 1956).

Varidase would therefore appear to be indicated in the treatment of sinusitis where use can be made of its ability to liquefy purulent exudates.

Varidase can be used intramuscularly, instilled locally or given as buccal tablets (Miller *et al.* 1958).

As Varidase breaks down the limiting membrane around a focus of infec-

Varidase* supplied by Lederle Cyanamid Overseas Corporation USA, Copenhagen

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TABLE 2 *Number of sinus punctures carried out on the operated patients*

	Varidase Group	Control Group
Number of operated patients	5	8
Number of punctures before operation (total)	32	56
Average number of punctures before operation	6.4	7.0

TABLE 3 *Distribution by age of the original number of patients*

	Varidase Group	Control Group
7–19 years	6	4
20–39 years	7	5
40–59 years	10	11
60 years and above	8	10

TABLE 4 *Number of sinus punctures in the actual material before clinical recovery*

	Varidase Group	Control Group
5 punctures and under	20	12
Above 5 punctures	4	5
Total number of punctures	95	83
Average number of punctures	4.0	4.9

TABLE 5 *The sensitivity for penicillin of the bacteria obtained by sinus puncture*

Sensitivity	Varidase Group	Control Group
0	8 pt of which 2 op	4 pt of which 1 op
+	1 pt of which 1 op	4 pt of which 1 op
+ +	1 pt	0
+ + +	5 pt of which 2 op	8 pt of which 1 op

tion the possibility of spreading the infection is increased therefore in all infective conditions Varidase treatment *should normally be combined* with the simultaneous administration of a suitable antibiotic

MATERIALS AND METHODS

The Present Study

The material includes 61 patients with ages ranging from 7–81 years who from 1/1 1961 until 1/7 1962 have been admitted to the Fredriksberg Hospital's Department for Ear, Nose, and Throat Diseases or who have been under treatment in the same out patients department for sinusitis maxillaris The diagnosis has been confirmed by sinus puncture The material has been divided into two groups according to the date of birth

Group I included patients born on an even date *These were treated with* Varidase buccal tablets

Each tablet contains 10 000 units of streptokinase together with 2500 units streptodornase and each patient received 4 of these tablets daily

With regard to the above mentioned danger of spreading the infection 400 000 units per diem of Di penicillin (i m) were administered prophylactically simultaneously with the administration of buccal Varidase

Group II included patients born on odd dates This group was used as the control material They were treated similarly to group I inasmuch as they received Di penicillin 400 000 units daily

Both groups were in addition treated with sinus puncture and drainage a m Proetz on alternate days

The difference in the treatment of group I and group II was only that the former were treated *with Varidase buccal tablets*

As a criterion for the effectiveness of the treatment we used the time when clear water was seen after sinus irrigation

In addition we attempted with as many patients as possible to carry out a control puncture 8 days after the above mentioned time but several of the patients did not meet to the required control

TABLE 1 *Original number of patients also patients excluded from the material*

	Varidase Group	Control Group
Complete number of patients	31	30
Number of operated patients	5	8
Excluded from the material (Treatment not completed)		5
Remaining number of patients	21	17

ZUSAMMENFASSUNG

61 Patienten mit klinischem verifizierten Sinusitis Maxillaris waren nach dem Gebohr in eine Behandlungsgruppe von 31 und eine Kontrolgruppe von 30 Patienten eingeteilt

Als einziger Unterschied der Kontrolgruppe war der Behandlungsgruppe 4 Varidase Resorbletten taglich gegeben Die beide Gruppen waren mit Penicilin und Sinus Punctur und Drainage a m Proetz behandelt

Der Zeitpunkt, wenn ein klares Waschwasser bei Sinus Punctur erhaltet war, wurde als ein Kriterium fur die Effektivitat der Therapie benutzt

Im vorhandenwarenden begrenzten Patientenmaterial hat man gefunden dass die mit Varidase behandelte Gruppe einen geringeren Mittelzahl Puncturen und weniger operierte Patienten als in der Kontrolgruppe zeigte

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DISCUSSION

By grouping according to the date of birth we have attempted to obtai two groups of patients which can be compared as directly as possible N differentiation has been made between acute and chronic sinusitis Thes must be considered as being equally represented in both groups

Table I shows the original number of patients in each group also th number of patients which were excluded from the actual material owin to operation or because the patients did not complete the initiated treatmen It should be noted that 3 patients (2 in the Varidase-group and 1 in the contro group) were excluded from the material in the start owing to possible pen cillin allergy.

Table II shows the number of operated patients It can be seen from th table that there is no difference in the average number of sinus puncture in the two groups before it was considered necessary to treat these patien operatively.

Table III shows that the distribution by age is similar in both the test an control group

Table IV shows that the difference between the average number of punc tures in the two groups is nearly one, which according to the original schedul of treatment corresponds to 2 days less illness in the Varidase treated group Despite the fact that penicillin was given prophylactically owing to the treatmen with Varidase, the possibility cannot be excluded that the penicillin-treatmen has influenced the obtained results Therefore, with the first sinus punctur pus was sent from all the patients to bacteriological examination and sens tivity test with special regard to the bacteria's sensitivity for penicillin

Table V shows the result of these tests A possible penicillin effect will a seen from the table favour the control group as there was in this group com paratively less patients with penicillin resistant bacteria in the irrigatio water That all patients cannot be seen in table V is owing partially to th fact that there was no growth during bacteriological examination, partially that the material in a number of cases was not suitable for sensitivity tes owing to subtilis contamination

We have not, in this small material found any significant effect of Varidase buccal tablets in the treatment of sinusitis maxillaris, but have as noted found on the average a smaller number of punctures—and herewith days o illness in the Varidase treated group We have also a smaller number o operated patients in the Varidase treated group

As the Varidase effect is less pronounced than would be expected this can possibly be explained by the fact that the membranes of the sinus—at least in the case of chronic sinusitis—often shows considerable variations from normal They are thickened possibly with polypoid degeneration and badly vascularised This should mean a reduced effect of the buccally administered Varidase One could expect in this case a greater effect of local treatment with Varidase by installation of Varidase in the sinuses

Side effects of Varidase have not been noted

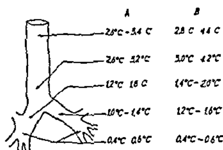


Fig 1 The range of temperature at different points of the tracheobronchial tree—(A) before and (B) during inhalation of smoke

adrenaline) Measurements of one minute duration were made in the following sites of the respiratory tract (*a*) Five cm below the tracheostoma (*b*) just above the bifurcation of the trachea (*c*) in the right and left main bronchus and (*d*) in the segmental divisions of the bronchial tree

After these measurements were completed a lighted cigarette was connected with the tracheostoma by a rubber tube The frequency of smoke inhalations was two per minute Five minutes after starting these inhalations all the above measurements were repeated

Our observations on the measurements of the eleven patients were as follows

Observation 1 —The range of temperature at different sites of the tracheo bronchial tree varies being smaller in its lower part This phenomenon was observed before and during the inhalation of smoke (Fig 1)

Observation 2 —The range of temperature during the inhalation of smoke was larger than before and more obvious in the recordings done nearer the tracheostoma (Fig 2)

Observation 3 —The average temperature in each of the above mentioned points during smoking was higher than before smoking This difference was more obvious in the peripheral parts of the tracheobronchial tree

The limited number of the examined cases does not permit a statistical analysis of the obtained data It is our intention to continue this experimental work on a larger number of laryngectomized patients as well as in a control serie of normal and tracheotomised patients

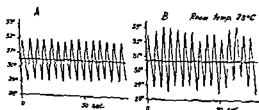


Fig 2 The range of temperature (A) before and (B) during inhalation at a point in the trachea just above bifurcation Laryngectomized patient

REMARKS ON TRACHEOBRONCHIAL TREE TEMPERATURE DURING CIGARETTE SMOKING

Preliminary Report

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A study of temperature variations in different parts of the tracheobronchial tree before and after cigarette smoking is presented.

In the last ten years several papers appeared dealing with the subject of the variations of temperature of the respiratory tract. The results, although different between themselves, contributed to the explanation of some problems of the physiology of respiration.

The differences in these results can be attributed to various factors affecting the temperature measurements. The method in use, the sensitivity of the recording equipment, the number of patients, their health condition and their reactions during measurements and the temperature of the room, all constitute factors that should be uniform in order to obtain reliable and standard results.

We faced even greater difficulties when trying to make temperature measurements along the respiratory tract under the influence of cigarette smoking.

Our observations were done on laryngectomized patients since their anatomy gives an excellent opportunity for the study of the physiology of respiration.

MATERIAL AND METHODS

Temperature measurements of the respiratory tract were done on eleven laryngectomized male, adult patients with a sensitive electronic thermometer, "Tastomet". The room temperature was 23°C.

The measurements were made with the patient in the sitting position. Body temperature and respiration rate were checked. During the whole procedure the trachea was anaesthetised with pantocaine 1 % (without

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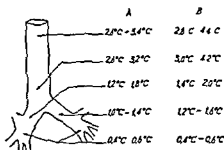


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The limited number of the examined cases does not permit a statistical analysis of the obtained data It is our intention to continue this experimental work on a larger number of laryngectomized patients as well as in a control serie of normal and tracheotomised patients

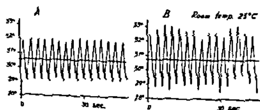


Fig 2 The range of temperature (A) before and (B) during inhalation at a point in the trachea just above bifurcation Laryngectomized patient

ZUSAMMENFASSUNG

Temperaturmessungen wurden bei laryngektomierten Patienten vor und nach Zigarettenrauchen in verschiedenen Teilen des tracheobronchialen Baumes vorgenommen Es liessen sich Temperaturanderungen verschiedenen Grades nachweisen

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TRANSCONIOSCOPY

A New Method of Laryngeal Investigation

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Determination of the extent of a pathological change on the lower aspect of the vocal cords and in the subglottic space is often of paramount importance for the choice of treatment (Muller 1954 Leroux Robert 1961) Since these regions cannot be inspected through a straight laryngoscope it has been necessary to introduce angle telescopes For various reasons the ordinary bronchoscopic telescopes (Dietzel 1953) are unsuitable In particular they easily come into contact with the mucosa which results in blurring of the image Introduction of Muller s laryngeal endoscope (Muller, 1954) has been considered as a great advance It is fitted with a 90° or 45° telescope which is protected from direct contact with the mucosa and thus permits inspection of the regions in question A drawback of the method is the limited visual field

At the Department of Otolaryngology Karolinska Sjukhuset a method denoted as transconioscopy has been devised according to a new principle A 90° telescope is inserted through a puncture in the cricothyroid membrane The equipment consists of a Storz antroscope i e a nasoscope with a 90° telescope and very great focal depth as well as a straight trocar with an inner diameter of 3 mm

The patient is placed in the tracheotomy position Xylocaine (0 5 ml) is injected subcutaneously in the midline over the cricothyroid membrane The membrane is punctured and 0 5–1 ml of tetracaine solution is deposited in the subglottic space A 4 5 mm horizontal incision is made in the skin and the trocar is introduced through it Using slight pressure the trocar is bored through the cricothyroid membrane Passage of the membrane is noticed at once by the cessation of resistance and a distinct click in the instrument The trocar is removed while the outer casing is held firmly with one hand and the telescope is inserted When the telescope is inserted perpendicularly to the longitudinal axis of the larynx the visual field corresponds to about ⅔ of the rima glottidis The instrument is highly mobile in the subglottic space and by manipulations in all the axes of rotation the lower aspect of the vocal cords the anterior commissure and the whole subglottic space can be inspected without any technical difficulty Owing to the great focal depth a sharp image is obtained in every position and the wide visual field is a great advantage

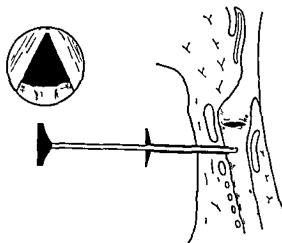


Fig. 1

Puncture of the cricothyroid membrane has been performed for many purposes, even with fairly large calibre instruments, and has proved to be unassociated with any severe complications (Ingelstedt, 1956). At our department, 22 patients have hitherto been examined with the technique described. None of them has had any subjective complaints during the examination. Afterwards, an area of subcutaneous emphysema, barely 15 mm in diameter, has been observed in several cases. No bleeding has occurred during or after the examination.

The examination in question seems to comprise a simple, accurate method for evaluation of anatomic and pathological changes on the lower aspect of the vocal cords and in the subglottic space.

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POSTURE AND CONGESTION OF NASAL MUCOSA IN ALLERGIC RHINITIS

Objective Measure of Effect of Specific Treatment

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In a series of untreated allergic rhinitis head low position with consequent increase of the hydrostatic pressure of the blood in the nose was followed by congestion of the nasal mucosa The increase of the nasal airway resistance was measured objectively and was found in 17 of 25 patients but not in healthy persons This increase of the airway resistance disappeared with the allergic symptoms after specific desensitization The underlying pathophysiological mechanism responsible for the mucosal congestion is briefly discussed Registration of this reaction of the nasal mucosa provides for the first time a simple test for objective evaluation of the effect of specific treatment of allergic rhinitis

In 1925 Sternberg showed that elevation of the pressure in the venous system of the head of experimental animals resulted in swelling of the nasal mucosa Some years later van Dishoeck (1938) found that compression of the jugular vein in man was followed by ipsilateral swelling of the nasal mucosa an observation he utilized in the elaboration of a technique for diagnosing venous sinus thrombophlebitis

In a previous publication (Ingelstedt & Runderantz 1964) a diagram was given of a probable pattern of the microscopical vascular network of the nasal mucosa which was based on data garnered from the literature and which warranted the conclusion that the dense subepithelial capillary net work is drained by deeper venous plexuses either directly via postcapillary veins or via large sinusoids The presence of these sinusoids within the mucosa of the inferior and middle turbinals and of the septum may explain the wide range of variation of mucosal swelling

The vasomotor control of the nasal mucosa is extremely complicated and not properly understood The generally accepted concept postulates the normal occurrence of a finely balanced interplay between sympathetic and parasympathetic impulses any preponderance of sympathetic impulses causing a contraction of the mucosal vessels any parasympathetic pre

The investigation was supported by grants from Alfred Osterlund s Foundation Sweden

ponderance causing vascular dilatation and congestion of the vascular network with consequent swelling of the mucosa.

Some investigators believe vegetative dystony to be an important factor in allergic disorders (Kuntz 1945 and 1950, Williams 1951). According to Kuntz "allergic rhinitis probably is invariably associated with a shift in the autonomic functional balance toward preponderance of the parasympathetic and cholinergic nerves. — The similarity of the appearance of nasal mucosa following sympathectomy to that of nasal allergy suggests that allergic disease and the autonomic nervous system may be intimately associated in a manner not yet discovered".

After surgical interference with the sympathetic ganglia of the cervical region many patients experience nasal obstruction, especially when in the recumbent position (*Millonig, Harris & Gardner* 1950, *Hamberger* 1961). Stuffiness of the nose in the recumbent position is also a well known side effect of hypotensive drugs, such as reserpine, used for ganglionic block (Connor, Kinard, Lord, McConn & Moyer 1957). The obstruction has been ascribed to engorgement of the nasal mucosa owing to the regional blockade with general dilatation or atony of the minor vessels draining the mucosa and the increased hydrostatic pressure in the recumbent position. It is also a commonplace that in allergic or vasomotor rhinitis nasal obstruction is more severe on retirement to bed. In the literature little, if any, attention has been given to the significance of venous hydrostatic pressure for the clinical symptoms of allergic and vasomotor rhinitis.

PURPOSE OF INVESTIGATION

If allergic rhinitis is associated with atony or dilatation of the venous network of the nasal mucosa, an elevation of the venous pressure in this network should result in congestion and swelling of the mucosa. The main purpose of the present investigation was to ascertain whether elevation of the hydrostatic pressure of the blood in the head in patients with allergic rhinitis leads to abnormal mucosal swelling and consequent obstruction of the nasal airways, and secondly, the effect, if any, of specific desensitization on such congestion.

METHOD

Mucosal congestion narrows the nasal cavities and thereby increases the air flow resistance. The air flow resistance during nose breathing was measured objectively with a special apparatus (*Allander & Ingelstedt*) capable of delivering a constant flow of air even on variation of the counter pressure within the nose between 0 and 100 mm H_2O (Ingelstedt & Rundcrantz 1964). In the present investigation a constant flow rate of 20 litres per minute was used.

The air flow resistance was measured at first with the subject sitting and then every other minute of a 20 minute period while he was lying on a bed

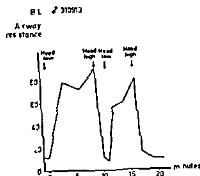


Fig 1

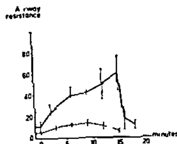


Fig 2

Fig 1 Effect of posture on nasal airway resistance in a patient with allergic rhinitis Airway resistance mm H_2O/20 litres/min

Fig 2 Mean nasal airway resistance in head low position during 15 minutes in a patient with allergic rhinitis before (continuous line) and after (broken line) specific treatment Each vertical represents range of measurements on three days Airway resistance mm H_2O/20 litres/min

raised at the foot end and forming an angle of 15° with the floor (head low position) and finally for some minutes with the head end of the bed raised 15° (head high position) This procedure was repeated several times

MATERIAL AND RESULTS

The material consisted of 20 healthy volunteers and of 25 patients with verified but untreated allergic rhinitis due to pollen (11 cases) and animal hair or house dust (14 cases) Change of posture from head high to head-low position never caused any significant increase in air flow resistance in the volunteers Nor was any noteworthy increase recorded in 8 of the allergic patients In the remaining 17 patients however the resistance increased markedly within a few minutes It soon disappeared on subsequent change over to the head high position The recordings were the same whether the subject was in the dorsal or supine position (Fig 1)

After 6 months treatment with subcutaneous injections of allergen 9 of the patients were reexamined Eight of these no longer had any symptoms of rhinitis and showed no abnormal increase of air flow resistance in the head low position Four patients suffered from hay fever exclusively during the pollen season When they were examined for the first time pollen were out of season and they had no symptoms of allergic rhinitis Yet nasal obstruction occurred in the head low position When reexamined, however, 6 months later during a new non pollen period but after having been desensitized these 4 patients no longer showed obstruction of the nose in head low position (Fig 2) The 9th patient a baker, who was continuously exposed to his allergens and in whom treatment had failed to produce the

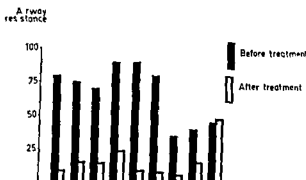


Fig 3 Nasal airway resistance in head low position in 9 cases of allergic rhinitis before and after treatment Airway resistance mm H_2O/20 litres/min

desired effect, the increase in air flow resistance in the head low position was the same as before treatment (Fig 3)

DISCUSSION

In 17 of 25 of the patients with untreated allergic rhinitis an increase of the hydrostatic pressure of the blood in the head by placing the patient in the head-low position resulted in an abnormally large increase in the resistance to the air flow through the nasal cavities This abnormal increase disappeared very soon on change over to the head-high position This rapid normalization of the air flow resistance appears to justify the conclusion that the increase in the resistance is due to vascular dilatation and not to extravascular escape of fluid

The pathophysiological mechanism of this obstruction of the nasal cavities in the head low position is not clear It may presumably be explained by a venous stasis combined with atony of the minor vessels including the sinusoids of the nasal mucosa Such vascular hypotonicity may be due to a preponderance of the parasympathetic autonomous system, which some investigators believe to exist in allergic rhinitis The desensitization thus seems to bring about a normalization of the tonus of the minor vessels of the nasal mucosa

We cannot explain why the head low position did not cause nasal obstruction in all patients with untreated allergic rhinitis Those patients who did not react did not differ from the others in sex, age allergens or duration of the disease

Objective and simple methods for measuring the effect of treatment of allergic rhinitis have hitherto been lacking Measurement of the resistance to air flow through the nasal cavities with the patient in various postures appears to enable objective assessment of treatment in those patients with allergic rhinitis, who have a positive posture reaction

ZUSAMMENFASSUNG

Eine Schwellung der Nasenschleimhaut, die durch Steigerung des hydrostatischen Blutdrucks verursacht wurde, zeigte sich in 17 von 25 Patienten mit unbehandelten

allergischen Rhinitiden Die Untersuchung wurde mittels objektiver Registrierung des Luftwegswiderstandes in der Nase durchgeführt Bei gesunden Personen konnte eine entsprechende hydrostatisch bedingte Anschwellung der Nasenschleimhaut nicht gefunden werden Nach Ausführung einer spezifischen Behandlung verschwand die Neigung zu hydrostatischer Schleimhautschwellung gleichzeitig mit den Symptomen der allergischen Rhinitis Die Pathophysiologie der hydrostatisch bedingten Schleimhautschwellung wird in aller Kürze diskutiert Die Registrierungen dieser Nasenschleimhautreaktion scheint eine einfache Methode zur objektiven Beurteilung der Behandlung allergischer Rhinitiden werden zu konnen

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TOPICAL ANESTHESIA FOR BRONCHOSCOPY

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Topical anesthesia in combination with some kind of sedation is probably the most common anesthetic procedure for bronchoscopy today Anesthetic agents are rapidly absorbed from the tracheobronchial tree They are all toxic and can cause manifest toxic reactions usually due to absolute or relative overdosage Measures to prevent complications and to treat toxic reactions are discussed

Bronchoscopy has come to play a leading role as an aid to diagnosis and treatment of pathological conditions in the tracheobronchial tree However, as with other surgical measures, it is often accompanied by discomfort and risks for the patient This discomfort can be relieved, and these risks diminished by great care in the examination, by an increased knowledge of anesthesia for bronchoscopy and of its complications What makes the problem particularly difficult is that topical anesthesia *in itself* can give rise to severe complications According to Chevalier-Jackson it must be our aim to find the method which brings about the greatest " safety, efficiency and comfort "

In Scandinavia the local anesthetics which are most commonly used for topical anesthesia in the tracheobronchial tract are the following

(1 Methyl 2 piperidincarbon) 2,6 dimethylanilid Carbocain Thesal® Bofors

2 Diaethylaminoaethyl 4 amino 3 butoxybenzoat hydrochlor Novesin®, Wander

Tetracaini hydrochloridum Tetrakain®, ACO

ω diethylaminoacet 2,6 xylidid (hydrochlorid) Xylocain 4%® Astra

In principle most local anesthetics exert the same effect on the organism There are, however, differences in *time of onset, duration, extension* and *degree* of anesthesia these properties can be included under the heading of the effectiveness of each local anesthetic in relation to its toxicity Unfortunately there *are no good* methods *for the determination* of topical anesthetic efficiency in the tracheobronchial tree It is uncertain if anesthetic evaluations on the cornea of the rabbit, for example can be applied to mucous membranes in the trachea *and bronchi*

It should be emphasized that there is a much more *rapid absorption* of

topical anesthetics from mucous membranes in the respiratory tract than from subcutaneous and intramuscular tissues There are also great differences in the rate of absorption from the different mucous membranes of the respiratory tract and esophagus themselves The rate of absorption increases in the following order

esophagus—pharynx—nose—larynx—trachea and bronchi—small bronchi and pulmonary alveoli

It has been stated that when the topical anesthetic reaches the pulmonary alveoli the absorption occurs with great rapidity and blood concentrations comparable to those after an intravenous injection are reached (Adriani & Campbell 1956 Astrom & Persson 1961)

COMPLICATIONS

When the toxicity of local anesthetics used for topical anesthesia was recognized it was noticed that there was a predominance of complications when the anesthetic was used in the nose throat and bronchi It was also clear that the complications were not caused by the surgical intervention but by an overdosage of the topical anesthetic When the anesthetic was used in high concentrations and on mucous membranes the suggested doses were too high for the administration in a region with a rapid absorption Maximum doses had been used which were based on studies using subcutaneous and intramuscular routes of administration with relatively slow absorption

Many single cases of toxic reactions after topical anesthesia have been reported but only a few surveys of larger numbers of cases have appeared (Mayer 1924 Klotz 1929 Carabelli 1952) They make the following points

Toxic reactions can occur sporadically and unexpectedly They are so infrequent that no physician who uses topical anesthetics has experience of many cases Complications are not regularly reported and thus our knowledge of the frequency of toxic reactions is limited although many anesthetists would admit to having seen more Many bronchoscopists admit privately the use of quantities exceeding the maximum recommended dose Toxic reactions are due to an overdosage but very often the quantity administered has not been known

Important information such as the chemical state of the anesthetic solution and autopsy records of fatal cases have usually not been published As many complications are not reported and slight reactions probably not always observed it is difficult to indicate the frequency of toxic reactions Large series without complications have been published (Harken & Salzberg 1948 Carabelli 1952 Titche 1961) Himalstein (1949) had 7 toxic reactions in 394 endoscopies Sadove *et al* found a frequency of 18 of toxic reactions in 2100 cases of topical anesthesia Weisel & Tella (1956) in a series of 1000 bronchoscopies with tetracain reported 19 cases of complications of which 7 had convulsions The highest incidence of complications has been reported after topical anesthesia with tetracain and the next most

TOPICAL ANESTHESIA FOR BRONCHOSCOPY

Alf Axelsson
Gothenburg, Sweden

From the Department of Otolaryngology (Head Prof G Herberts), Sahlgrenska Sjukhuset, Gothenburg

Topical anesthesia in combination with some kind of sedation is probably the most common anesthetic procedure for bronchoscopy today Anesthetic agents are rapidly absorbed from the tracheobronchial tree They are all toxic and can cause manifest toxic reactions usually due to absolute or relative overdosage Measures to prevent complications and to treat toxic reactions are discussed

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frequent with cocaine These two anesthetics are probably the two most extensively used and thus it cannot be concluded that they are more toxic than others Only one single toxic reaction has been reported after topical anesthesia with Novesin and none with Xylocain A survey of the literature indicates that tetracain is the most dangerous anesthetic agent but also the most effective one

Several experiments have been performed to establish the toxicity of local anesthetics (Luduena *et al* 1958 Åstrom & Persson 1961) In general this has been done by the determination of minimum or mean lethal doses in animals From the clinical viewpoint a determination of the toxicity must be compared with an examination of the anesthetic efficiency The values found must also be considered in relation to the rate of administration the concentration of the anesthetic and the species of animals etc The use of higher quantities than are used in clinical practice as well as the doubtfulness about the relevance of animal experiment for man make it difficult to draw any certain conclusions from many published investigations The general trend points to a parallelism between increased anesthetic efficiency and increased toxicity (Luduena *et al* 1958)

Symptoms of Toxic Reactions

These symptoms are the result of an excessive blood concentration of the anesthetic and its influence on the different systems mentioned in Table I

A Effects on central nervous system

In case of a moderate overdosage the patient becomes nervous and anxious and has tremors In more severe cases of overdosage all local anesthetics are convulsant because of their stimulating effect on the central nervous system In such a case the patient first has palpitations then he becomes unconscious and has general clonic seizures Small doses of local anesthetics on the contrary have an anticonvulsant effect on the brain This has been used to advantage in the treatment of epileptic seizures The local anesthetics can relieve the seizure either by a single dose or by continuous intravenous infusion (Sorel & Lejeune 1955 Bernhard Bohm & Wiesel 1956 Frey 1962)

B Effects on respiration

In case of a moderate overdosage the patient gets an increased respiratory rate because local anesthetics may have a stimulating influence on the respiration In cases of more severe overdosage the local anesthetics have a depressive influence on the repiratory centre such that the respiratory rate is decreased and the respiration becomes insufficient The effect of increasing anoxia very rapidly adds to the effect of the local anesthetic on the respiratory centre and thus respiratory failure may supervene The importance of maintaining free air ways and instituting artificial respiration thus is clear

TABLE I *Influence of local anesthetics on respiration, circulation, and central nervous system*

Influence on	Moderate doses	Large doses
Brain	Anticonvulsant action	Nervousness Tremor Convulsions
Respiration	Increased respiratory rate	Irregular breathing Respiratory failure
Circulation	Vasoconstriction Raised blood pressure Increased heart rate	Vasodilatation Lowered blood pressure Syncope Arrhythmias Cardiac failure

(Shumacker 1941, Adriani & Campbell, 1956, Moore & Bridenbaugh, 1960)

C Effects on circulation

In moderate doses local anesthetics also increase the heart rate and elevate the blood pressure In cases of a more severe overdosage again the local anesthetics have a depressive influence on the vital medullary centres This may coincide with a decreased irritability of the myocardium and vasodilatation The result is a fall of blood pressure, arrythmias and even asystole

In cases with very high blood concentrations after a severe overdosage, or rapid absorption symptoms of excitation may be absent, and instead there is a sudden collapse with unconsciousness and respiratory failure, which may be rapidly followed by asystole if not treated (Shumacker, 1941)

D Hypersensitivity

The cause of toxic reactions is nearly always absolute or relative overdosage However local anesthetics in low concentrations may cause allergic manifestations Some authors even consider the toxic reactions to be of allergic origin an opinion which has been questioned by some (Sadove *et al*, 1952 Adriani & Campbell 1956 Moore & Bridenbaugh 1960) Allergic symptoms can be of different kinds such as dermatitis, urticaria eczematoid lesions of various types and occasionally oedema of mucous membranes Patients with asthmatic disorders constitute a group of susceptible individuals Another explanation of toxic reactions which is not easily assessed is high individual variation in *sensitivity* to topical anesthetics not of allergic type A susceptible individual thus tolerates much less of the substance than a normal one Particular care must be taken in all cases where the patient is for any reason considered to be bad risk (Gordh, 1949)

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(Rubin 1951) To ascertain how epinephrine affects the toxicity many experiments have been performed which indicate that when administered by a subcutaneous or intramuscular injection it prolongs the absorption of local anesthetics by vasoconstriction (Keil & Vieten 1952 Riesser & Ther 1953 Schmidt 1959) On the contrary however when epinephrine and local anesthetics are rapidly absorbed as following intravenous injection or in topical anesthesia from the bronchi or other highly vascular mucous membranes it has been reported to increase the toxicity (Rubin 1951 Steinhaus 1952 Adriani & Campbell 1956) In this case the addition of *epinephrine* to a topical anesthetic does not permit the administration of higher doses In addition in case of overdosage with a topical anesthetic the possibility arises of a coexisting overdosage with epinephrine Unfortunately the symptoms after a toxic dose of epinephrine are similar to those after a mild overdosage of local anesthetics The patient exhibits *anxiety pallor tremor,* tachycardia precordial pains tachypnoea and raised blood pressure In severe cases the patient may die from acute dilatation of the heart *pulmonary* oedema or auricular fibrillation These serious symptoms are not part of the pattern of an overdosage with a topical anesthetic In this connection the increased risk of use of epinephrine in patients with coronary sclerosis must be remembered Series have been published of a larger number of bronchoscopies where the topical anesthetic was used *without vasoconstrictor* agents and where no toxic complications appeared (Hancock 1939 Ireland *et al* 1951 Carabelli 1952) Some authors have recommended the *administration* of *analeptic agents* as a treatment of complications (Klotz 1929 Jackson 1949 Fischer 1953) but the general view is that they are of no value or even contraindicated (Knoefel *et al* 1930 Shumacker 1941 Sadove *et al* 1952 Schmidt 1959 Moore & Bridenbaugh 1960)

If there has been some hesitation in using *epinephrine* barbiturates and analeptic agents there is a general agreement about the use of *oxygen and artificial respiration* in clinical complications (Gordh 1949 Himalstein 1953 Jackson 1949 Steinhaus 1952 Adriani & Campbell 1956 Sadove *et al* 1955 Moore & Bridenbaugh 1960) In many animal experiments it has been possible to demonstrate that correct administration of oxygen during toxic reactions of *differing* severities has been able to delay or avoid death of the animals *During* convulsions it is consequently of the greatest *importance* to *maintain* a good oxygen supply Respiration of the patient by manual pressure on the anesthetic bag may not give enough ventilation partly because of laryngospasm and partly because of clonic contractions of the respiratory muscles The *resulting* hypoxia must be completely overcome because it adds to the depressive action of local anesthetics on vital *medullary* centres Intubation and artificial *respiration* consequently should be started at once It must also be emphasized in this connection that oxygen must be supplied during bronchoscopy under topical *anesthesia* in cases when the patients probably have a hypoxia or the ventilation is prevented by an obstructive or restrictive pulmonary disease

The Prevention and Treatment of Complications

The observation of toxic reactions after topical anesthesia naturally has provoked interest in finding different measures *to reduce the frequency of* untoward reactions Besides the different rate of absorption from different mucous membranes, the absorption also depends upon the rate of administration, the concentration of the anesthetic and the addition of agents with a vasoconstrictor action If local anesthetics are given in *divided doses* the frequency of reactions are diminished A slow administration of divided doses leads to prolonged absorption and lower blood concentrations (Klotz 1929, Rubin, 1951, Sadove *et al*, 1956, Schmidt, 1959)

Some authors have claimed that the toxicity is dependent upon *the concentration of the anesthetic* For example a 2% solution could be absorbed more rapidly than a 1% solution, and thus apparently have more than twice the effect Several experiments have demonstrated, however, that the blood level is only dependent upon the total amount of anesthetic administered, provided the solutions are given under similar conditions in other respects (Klotz, 1929, Rubin, 1951, Sadove *et al*, 1952)

As mentioned above all local anesthetics can have a convulsant effect on the central nervous system In 1929 it was found that seizures caused by the local anesthetics could be eliminated by *barbiturates* (Hofvendal) Short acting barbiturates are now a generally accepted treatment of convulsive complications The quantity of barbiturate should not, however, exceed the dose which suppresses the seizures If a heavy dose of barbiturate is given the depressive action on vital medullary centres can add to the corresponding depressive action of local anesthetics on these centres and the result may be deleterious (Sadove *et al*, 1952) Some experiments have demonstrated that the protective action of barbiturates is reduced in the presence of a high concentration in blood of local anesthetics (Shumacker, 1941) Probably the barbiturates also have a prophylactic action against toxic reactions of local anesthetics in normal dosage This fact, and the necessity for a sedated patient make the use of barbiturates as premedication justifiable Muscle relaxants such as succinylcholin have also been used successfully for the treatment of seizures (Moore & Bridenbaugh, 1960)

Attempts have been made to reduce the absorption and turnover in the blood of topical anesthetics by the addition of different substances with *vasoconstrictor action* Thus it should be possible to use solutions of lower concentrations and get a prolonged anesthesia Epinephrine is the agent most commonly used Many authors consider the addition of epinephrine to be of value in preventing toxic complications (Eggleston & Hatcher, 1919, Fussgänger & Schaumann, 1931 Shumacker, 1941, Derbes & Engelhardt, 1944, Jackson, 1949 Jacoby, 1951, Carabelli, 1952 Titche, 1961) However, it has been *disputed whether epinephrine reduces the absorption* and diminishes the toxicity (Hancock, 1939, Fischer, 1953)

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particular mucous membrane has its particular conditions of absorption Local anesthetics in small doses have a stimulating effect on the vasomotor and respiratory centre and an anticonvulsant effect on the cortex In high doses they have a reverse action on the vasomotor and respiratory centres and a depressant action on the myocardium In high doses they cause convulsions

There is reason to believe that complications with topical anesthesia particularly in the tracheobronchial tree are by no means uncommon Often they have appeared unexpectedly and the treatment has not always been the correct one Almost all reactions have been due to overdosage but the rapidity of administration plays an important role and slow administration may give less risks than rapid administration In those cases where a heavy overdosage and rapid administration combine collapse can occur without preceding convulsions

The addition of vasoconstrictor retards absorption of local anesthetics in regions of poor vascularity If the absorption is rapid as in highly vascularized areas or due to overdosage, epinephrine can increase the risk of complications and impair the prognosis in an already evident toxic reaction Used properly a topical anesthetic probably needs no addition of vasoconstrictor agents in anesthesia for bronchoscopy

Every physician performing laryngo bronchial examination should be acquainted with techniques of the topical anesthesia Weak solutions should be used in quantities not exceeding the maximum dose The dose administered should be noted However, the quantity absorbed is uncertain as the patient may cough up spit out or swallow some of the anesthetic

The following list is a suggested scheme for topical anesthesia for bronchoscopy It is a result of a survey of the literature on topical anesthesia for bronchoscopy

Outline for the topical anesthesia for bronchoscopy

I Preparation

Establishment of rapport with the patient Explanation of the procedure

Premedication Atropine or scopolamin + small doses of hypnotics or sedatives

The topical anesthetic solution An exact quantity, less than the maximum dose is poured into a graduated tube without vasoconstrictor agents The weakest concentration is recommended

Current maximal doses (Manufacturers in recommending the doses, generally disregard premedication the different absorption from different mucous membranes and do not stipulate an exact dose of vasoconstrictor agent)

%	*With vasoconstrictor*	*Without vasoconstrictor*
	Carbocain Thesat®, Bofors	
(1 1)	15 cc (epinephrine)	45 cc
	Novesin®, Wander	
1	10 cc (cyklosan 1 %)	10 cc

To counteract a fall in blood pressure in toxic reactions different agents with a *vasopressor action* can be recommended (Gordh 1949 Adriani & Campbell 1956 Sadove *et al* 1956 Moore & Bridenbaugh 1960) If the anesthetic solution has been given with epinephrine this substance should be avoided as it is probably already present in the blood in high concentration

Methods of Topical Anesthesia

There are many anesthetic procedures for bronchoscopy Different premedications are recommended e g barbiturates alkaloids or antihistamines The topical anesthetic used also varies as does the concentration of the anesthetic Some prefer a greater amount of a dilute solution others a smaller amount of a more concentrated one The method of administration of the topical anesthetic varies widely administration of the anesthetic with spray dripping it on the mucous membranes a combination of these two procedures applying the swabs soaked in anesthetic to the pyriform fossae inhalation of nebulized anesthetic solutions injection of the anesthetic through the cricothyroid membrane among others It is very difficult to ascertain whether one method is superior to another without objective comparison It is important that the bronchoscopist becomes accustomed to the method and to the anesthetic he uses and that he takes every precaution It is also important to use the weakest solution that permits a good anesthesia in the laryngobronchial tree This is because a certain volume of anesthetic solution is needed for the anesthesia regardless of its concentration These are no great problems for the experienced bronchoscopist but a physician who has little experience of anesthesia for bronchoscopy sometimes uses a greater quantity of a topical anesthetic It is often wise for the bronchoscopist to check the dosage of the anesthetic before its use The maximum dose for tetracain without vasoconstrictor for example is 20 mg which corresponds to 1 cc of a 2% solution One further cc thus means twice the maximum dose of tetracain A weaker anesthetic which has a greater maximum dose can be held more easily within the safety margins and one cc more than the recommended maximum dose of such an anesthetic also is much less dangerous

In some cases it is preferable to have less deep anesthesia during bronchoscopy as for example in cases of a pulmonary atelectasis due to stagnation of bronchial secretion With adequate cough reflexes there is a good possibility that the secretion can be coughed up and be aspirated during the bronchoscopy

CONCLUSION

Local anesthetics in concentrations used for topical application are rapidly absorbed from mucous membranes particularly from the larynx trachea bronchi and pulmonary alveoles The rate of absorption increases as the agent reaches further down into the bronchial tree The differences in rate of absorption are so great that one should speak of anesthesia of esophagus larynx or bronchi rather than use the general term topical anesthesia Each

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%	*With vasoconstrictor*	*Without vasoconstrictor*
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(1 1)	4 5 cc (epinephrine)	4 5 cc
	NOVESIN®, Wander	
1	10 cc (cyklosan 1 %)	10 cc

		TETRACAIN®, ACO	
1–2	—		20 mg = 2 – 1 cc
		XYLOCAIN®, Astra	
4	12.5 cc (epinephrine)		5 cc

II Anesthetic procedure

1. Insertion of an intravenous needle for injection in the case of subsequent complications
2. Application of the anesthetic to the different mucous membranes at intervals for about 10 minutes in divided doses, an exact calculation of the dose for every region is desirable
3. Administration of the anesthetic only in the regions where it is needed for the accomplishment of the bronchoscopy
4. Recording of the quantity administered
5. After administration of drug the patient is placed on the operating table under supervision
6. The complete anesthetic effect usually takes about 10 minutes

III The bronchoscopy

Careful bronchoscopic technique. Conversation with the patient to maintain confidence. Check pulse and blood-pressure

IV Complications

Equipment which should be available in the bronchoscopy room

Equipment for intubation and cardiac massage
Aspiration apparatus
Syringes and needles
Pharyngeal tube
Anesthesia apparatus
Short-acting barbiturates
Narkotal®, Astra, Pentothal sodium®, Abbott
or Muscle-relaxants
Succinylcholin Celocurin®, Vitrum, Sucolin®, Allen & Hanbury
Agents with vasopressive action
Aramine®, MSD, Neosynephrine®, Winthrop

Measures in case of slight reactions

Stop the anesthetic procedure or the bronchoscopy immediately. Administer oxygen at high flow rate and place the patient in a recumbent position. Vasopressive agents if needed

Severe reactions

If the patient has *convulsions*,

1. Artificial respiration with oxygen by mask should be started
2. Short acting barbiturates or muscle relaxants should be given to suppress convulsions, leaving the needle in place in case convulsions should recur
3. Intubation should be performed as soon as possible for artificial respiration
4. Vasopressor agents and intravenous infusions should be given if collapse occurs
5. External cardiac massage

ZUSAMMENFASSUNG

Die Oberflächen Anästhesie der oberen Luftwege ist wahrscheinlich immer noch die gewöhnlichste Anästhesieform bei der Bronchoskopie Jedoch hat die starke Resorption der Lokal Anästhetika besonders in den Bronchen viele schwere toxische Erscheinungen mitgebracht Bei einer leichten Überdosierung werden die Respirations und Zirkulationssysteme und das zentrale Nervensystem gereizt bei einer schweren Überdosierung dagegen werden diese Organsysteme gelähmt Bei einer sehr schnellen Resorption können die Symptome der Reizphase völlig ausbleiben und das toxische Bild zeigt sich dann als Kollaps Wahrscheinlich hat die Ausführung der Anästhesie an sich nicht so grosse Bedeutung wichtiger ist dass man an eine Methode und an ein Anästhetikum gewöhnt ist Um toxische Erscheinungen zu vermeiden muss möglichst wenig Anästhetikum verwendet werden es muss langsam und mit Pausen verabreicht werden Wahrscheinlich bietet der Zusatz von *Vasokonstriktoren keinen* Vorteil bei der *Anästhesie in den Bronchen* Bei einer manifesten Komplikation muss sofort künstliche Atmung mit *Sauerstoff gegeben* werden Bei Krämpfen gibt man bis zu deren Abklingen kurzwirkende Barbiturate

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CYTOPLASMIC BASOPHILIA IN SPIRAL GANGLION CELLS OF THE GUINEA-PIG FOLLOWING STRONG ACOUSTIC STIMULATION

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Forty five anesthetised guinea pigs were subjected to white noise at a level of 127 db for one hour, as a free field stimulus At intervals of from 0 up to 31 days after the application of the stimulus, the animals underwent autopsy and were examined by cytophotometry for the degree of cytoplasmic basophilia in the cells of the spiral ganglion, following staining by gallocyanin-chrome alum at pH 1 64, to indicate the relative changes in RNA content The ganglion cells were also measured for possible changes in size An initial fall in the cytoplasmic basophilia was found, but in the course of two weeks this gradually returned to normal values, as indicated by nine control animals No significant change in cell size could be found which might be ascribed to the acoustic stress It was further concluded that guinea pigs could tolerate an acoustic stimulus of this magnitude, and that ganglion cell degeneration, previously observed following shock waves of the same intensity must be secondary to destruction of the organ of Corti

INTRODUCTION

The biochemical changes occurring in the cytoplasm of ganglion cells following specific stimulation of the appropriate sense organs have been studied particularly in the peripheral ganglia and nuclei of the eighth cranial nerve (Hydén 1961) Studies have also been made on the retinal ganglion cells following physiological stimulation with daylight, using methods more or less identical with the one employed here (Bech, 1957)

The inner ear is a very suitable organ for studying the reaction of peripheral ganglion cells to a stimulus of a physiological nature, as the receptor organ consists of only one link (the hair cell) whose isolated function can be studied by the methods of histomorphology, electrophysiology, histochemistry and autoradiography (Vosteen, 1961) The spiral ganglion consists of a large number of bipolar cells, regular in shape, in many respects of uniform appearance, and of an easily determined size The Nissl substance is distributed fairly uniformly, so that cytomorphological measurements can be made Light microscopy suggests that the cells are uniform in type, but electron microscopic studies seem to indicate that in rats two types can be distinguished (Rosenbluth 1962)

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The specific stimulus employed (tones or noise) is easily measurable and adjustable as to dosage, and the experimental animal can survive the experiment. The function of the peripheral organ of hearing is unaffected by training and general state of health.

In a previous study the technique of gallocyanin chrome alum staining and cytophotometry of the nerve cells of the spiral ganglion in the guinea pig were employed to show that the acoustic stimulus of white noise at a level of 127 db for periods of 30 minutes to 6 hours resulted in up to 25% reduction in the *cytoplasmic basophilia occurring immediately* following the application of stress and not involving any change in cell size. No relationship was found between the reduction in basophilia and the duration of the noise (Thomsen & Pakkenberg 1962). The aim of the present study is to examine the variation in cytoplasmic basophilia throughout a period of 0–31 days following an acoustic stress of 127 db white noise for 1 hour using the same gallocyanin chrome alum staining technique, thus making it possible to record any changes in the RNA concentration of the cells (Einarson 1960).

MATERIAL AND METHODS

Fifty four guinea pigs from the same stud, weighing 200–300 g and including 9 control animals, were used in the experiments. Prior to the experiments they had lived in quiet surroundings with low noise level. None showed any sign of middle ear inflammation at autopsy. The auditory vestibular function was tested by Preyer's reflex and by examining their postural reflexes. Under Nembutal anaesthesia (15 mg/kg), thus abolishing Preyer's reflex, they were placed in a funnel shaped wooden box covered with sound insulating board. The animals lay on a heating pad in the prone position with head fixated. The sound was applied as a free field stimulus by means of a loudspeaker placed in the lid of the box at a distance of 35 cm from the animals. The acoustic stimulus was produced by amplifying the masking noise from an M. P. Pedersen audiometer (Type B 220 (T no. 9) to a total intensity of 127 db. The frequency analysis of the noise, measured in db above $2 \cdot 10^{-4}$ bar/⅓ octave, showed quite a uniform spectral distribution over the frequency range 400–5000 c/s (Fig. 1).

The animals were exposed to the sound stimulus for 1 hour and then observed on awakening from the anaesthesia. Hypoxia was not found. On awakening, which occurred ½–1 hour after termination of the stimulus, the hearing was tested by means of Preyer's reflex and the vestibular function checked. As soon as the animals showed normal behaviour, ate and made their usual sounds, a state which was normally reached 1–2 hours after the experiment, they were placed in their customary surroundings.

At regular intervals from 1 up to 31 days after the acoustic stimulation 3–4 animals were taken and tested for Preyer's reflex and postural reflexes and then intravital fixation was performed under urethane anaesthesia.

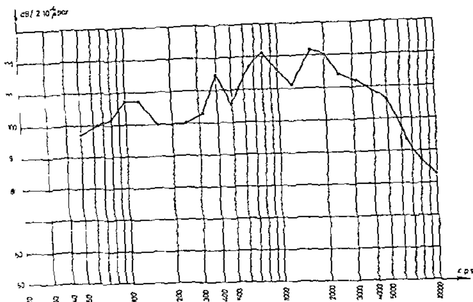


Fig. 1. Frequency analysis of the applied noise.

The vascular system was first perfused with NaCl solution 0.9% for ½ minute at a pressure of 67 cm of water through a cannula in the aorta draining from the right auricle; following this was perfused 95% alcohol. Profuse double sided nasal drip was taken as a sign of adequate perfusion. The animals were then decapitated, the bullae opened and then using the Zeiss operation microscope the apical turn of the cochlea was opened, at the same time luxating the stapes out of the oval window. After removing the cerebrum and cerebellum the preparation was fixed for 24 hours in 95% alcohol at 0°C. The modiolus was dissected out with the ductus cochlearis in place and in addition representative pieces of the ductus cochlearis and organ of Corti were dissected out as whole preparations. After a further 24 hours of fixation in 95% alcohol at 0°C the preparation was embedded in paraffin and cut in 10 μ slices parallel to the axis of the modiolus. The sections were stained by Einarson's gallocyanin chrome alum method at pH 1.64 for 48 hours and a temperature of 18°C and mounted in DPX. In each field the section thickness was determined by focussing on the upper and lower surfaces of the section. The extinction in the cytoplasm of the spiral ganglion cells was measured by means of a cytophotometer.

The cytophotometer consists of an Ortholux microscope (Leitz) which is used together with a Photovolt multiplier photometer model 520A with a multiplier tube 21C. The photometer is placed on a sledge 40 cm above the ocular. At the two extreme positions of the sledge there are respectively the phototube with a 4 mm diaphragm and an opal glass plate with an engraved circle 1 mm in diameter placed exactly in the optical axis of the microscope. An oil immersion objective of N.A.

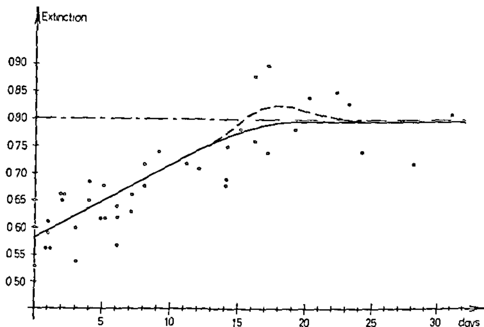


FIG 2 The extinction values of the nerve cells from the spiral ganglion following noise plotted against the survival time

1 32 is used with an ocular of ×15 magnification, so that the magnification on the opal glass plate is ×3000 The circle (and the diaphragm) correspond to a circular area of diameter 1 32 μ in the preparation Another opal glass is placed in front of the phototube to diffuse the light, as the sensitivity of the multiplier tube electrode is not the same centrally as peripherally in the measuring field An obliquely placed mirror above the sledge reflects the picture from the opal glass The microscope lamp is a tungsten lamp, 6 volt, 5 amp, supplied from the main supply via a voltage regulator Monochromatic light is used, wavelength 580 nm, provided by an interference filter Twenty-five cells were measured in each section, two measurements per cell The measurements were performed consecutively on every cell which satisfied the following conditions middle position in the section, and absence of cutting and dissection artefacts Control measurements showed that after the acoustic stimulus, the extinction was the same in cells lying apically and basally in the ganglion All measured extinction values were corrected for deviations of the section thickness from 10 μ In each animal, measurements were taken of the size of these approximately ellipsoidal cells by measuring the major and minor diameters on 20 cells (10 apical and 10 basal) The sum of these measurements served as a linear parameter to evaluate variations in cell size from animal to animal

A morphological study showed that the ganglion cells could be divided into two groups, possibly of significance as far as the measuring procedure for the extinction was concerned These were (1) cells with uniformly distributed Nissl granules, and (2) cells with Nissl granules placed peripherally in the cell, around a homogeneous perinuclear field In a number of preparations, a differential count was made in 100 cells apically and 100 cells basally in the ganglion, using the above criterion The significance of this irregular distribution is examined and discussed under the section on methods

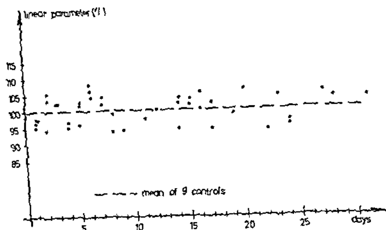


Fig 3 Relative linear cell size plotted against the survival time

Finally, a representative selection of whole preparations of the organ of Corti were examined with the object of observing results of the acoustic trauma (Neubert 1952 Beck 1956)

RESULTS

Fig 2 shows the result of the photometric measurements on 45 guinea pigs subjected to white noise at a level of 127 db for 1 hour, the histological preparations being made as described over a period of 0 31 days after the stimulus The dotted line shows the mean of the extinction value for 9 controls (Thomsen & Pakkenberg 1962)

The curve shows that a relative chromophobia develops immediately in the cells of the spiral ganglion The chromophobia gradually decreases over a period of 15 days then possibly develops into a slight chromophilic phase which in turn goes over to chromoneutrality

If the relative linear cell size is plotted against the appropriate survival time no correlation is apparent between these variables following the acoustic stimulation A change in linear cell size can thus not explain the chromophobia The small variations in the mean cell size from animal to animal are presumably the result of differences in speed of fixation (Fig 3)

Table 1 shows the differential count of two groups of nerve cells group N with uniformly distributed basophil granules and group F with granules arranged marginally around a homogeneous central part

It appears that during the first 24 hours there is a relative increase in the number of F cells from a normal 10 % to 20 % After the second 24 hour period however the normal percentage distribution reappears During the period from the 2nd to the 5th day, a rise in the number and size of nuclear caps is seen which might indicate accelerated RNA production (Fig 4)

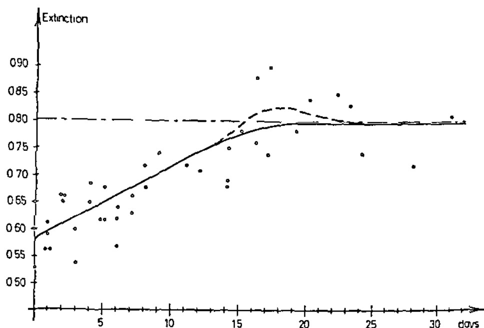


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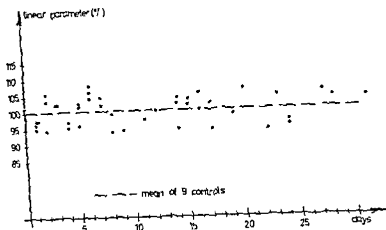


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Table 1 shows the differential count of two groups of nerve cells, group N with uniformly distributed basophil granules, and group E with granules arranged marginally around a homogeneous central part.

It appears that during the first 24 hours there is a relative increase in the number of E cells from a normal 10% to 20%. After the second 24 hour period, however, the normal percentage distribution reappears. During the period from the 2nd to the 5th day a rise in the number and size of nuclear caps is seen, which might indicate accelerated RNA production (Fig. 4).

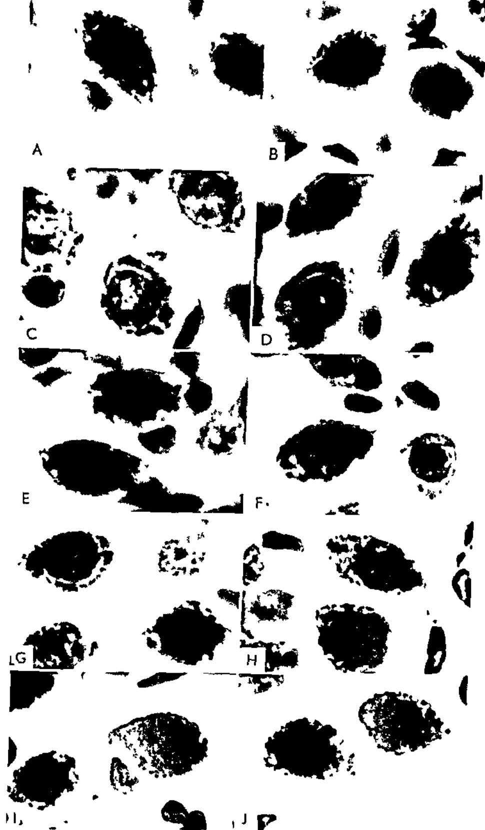


Fig. 1. Spiral ganglion cells in gallocyanin staining.
a Normal cells, second turn. *b* Normal cells, third turn. *c* One day after noise, second turn. I cells. *d* One day after noise, third turn. I cells. *e* Two days after noise, first turn, beginning nuclear caps. *f*, Two days after noise, second turn, beginning nuclear caps in I cells. *g* Three days after noise, first turn, nuclear caps. *h* Three days after noise, third turn, nuclear caps. *i* Fifteen days after noise, first turn, normochrome cells. *j* Twenty three days after noise, second turn, normochrome cells.



Fi   Selected hair cells from some of the 21 examined animals Gallocyanin
a Normal inner hair cells b Normal outer hair cells c, Two days after noise, inner hair cells second turn d Two days after noise outer hair cells second turn e Twenty-eight days after noise organ of Corti second turn f Two days after noise, Swellkern in outer hair cells, second turn g Thirty-one days after noise, organ of Corti, third turn No hair cell loss h, Thirty-one days after noise outer hair cells no hair cell loss

TABLE 1

No. of animals	Days after noise	% I. cells in apical turn	% I. cells in basal turn	Mean %	Nuclear caps present
1	Before noise	6	14	10	
2	0	16	22	19	–
4	1	14	24	19	
2	2	11	9	10	+
1	3	14	3	9	+
1	5	10	8	9	(+)
1	14	10	12	11	–
1	19	13	14	14	–
1	21	11	6	9	
1	28	9	3	6	–

Percentual number of nerve cells with irregular distribution of Nissl granula (I. cells). 200 cells counted in each animal.

A histological examination (whole preparation) of the organ of Corti in a total of 21 experimental animals did not give consistent results because of the difficulty of distinguishing artefacts in the delicate outer hair cells from changes produced physiologically. As a whole we have the impression of strong but reversible irritation of the outer hair cells. It seems that these changes are maintained longer—up to 2–3 weeks—than reported by other authors (Beck & Michler 1960); just as in our experiments the changes are not particularly localized to the inner row of outer hair cells (Fig. 5). In these preparations it is a constant and significant finding that there is in no case a decrease in the number of outer or inner hair cells or of ganglion cells after this very powerful stimulus. This corresponds well with the results of the acoustic examination which showed that animals kept alive for more than 10–14 days apparently regained normal hearing, although all experimental animals were totally deaf immediately after the acoustic stress, showing an abolished Preyer's reflex, the deafness decreasing during the next few days.

DISCUSSION OF METHODS

It has been demonstrated by numerous authors that Einarson's gallocyanin chrome alum staining is specific for RNA and DNA in nerve cells, most often by using protease free ribonuclease (Sandritter 1952, Beck 1957).

In a previous study one of the present authors confirmed the specificity by ribonuclease digestion, comparing the results obtained with those using toluidin and pyronine staining (Pallenberg 1958). Electron microscope studies of gallocyanin stained preparations before and after ribonuclease and deoxyribonuclease digestion have led to the same results (Mundlaur 1961).

A further main condition for the quantitative use of the method is that the dye should bind stoichiometrically to the substances to be measured. It has been shown that gallocyanin chrome alum binds to RNA and DNA in the proportions of $\frac{1}{3}$ and $\frac{1}{2}$ respectively at pH 1.64 (Sandritter, 1954). Further, parallelism has been demonstrated between cytophotometry following gallocyanin staining and UV spectrophotometry (Sandritter, 1955; Lagerstedt, 1948).

The acoustic stimulus employed was chosen as white noise in order to subject the entire organ of Corti and thus the spiral ganglion to a maximum stress, with the possibility that irreversible lesions are not produced in any particular region. A study of hearing and the inner ear, as well as the fact that the changes found are reversible, shows that the above requirement was satisfied. The stimulus was applied physiologically, and there can hardly have been any considerable sound loss through the relatively wide auditory meatus. The inhibitory effect both of the middle ear muscles and of the central impulses on the function of the first neurone was extinguished by the barbiturate anaesthesia (Perlman, 1960; Carmel & Starr, 1962; Starr & Livingston, 1963).

The photometer used was constructed according to the method of Pollister & Ris (1947). Because of the need to use monochromatic light and high magnification, the path of the rays was convergent, with a large numerical aperture. Theoretical considerations and experimental studies show that when the absorbing material is uniformly distributed throughout the medium being measured, it is possible to depart considerably from parallel illumination when making absorption measurements and still obtain true values for the relative amounts of material.

In fact, in the present investigation the material studied includes cells with an irregular distribution of RNA (marginally placed Nissl granules in F cells). There is therefore a possible source of error, namely that the extinction values in these cells give a false expression for the concentration, and thus a false value for the amount of RNA. Furthermore, as the number of F cells alters on stimulation of the ganglion, this might introduce an error even into these relative measurements. The following measurements show, however, that the above state of affairs had no influence on the values measured. Measurements were made of the absorption of white light (unfiltered light from the microscope lamp) in 48 cells with uniformly distributed RNA and in 36 cells with Nissl granules situated marginally in the cytoplasm. In each cell, the measurement was carried out with both parallel light and focussed light, the latter procedure being the same as that used in the case of monochromatic light, and thus giving measurement ratios identical with those between the monochromatic measurements (although less specific as to concentration*).

For each cell, a galvanometer deflection a_p was recorded corresponding to parallel illumination, and a deflection a_c corresponding to convergent illumination. a_p is a correct relative measure of the RNA concentration in

both cell types For each cell, the ratio $r = a_c/a_p$ can be calculated If this value is found to be constant within the range of measuring uncertainty and biological scatter, then a_c can also be used as a correct relative measure of the RNA content, and the possible source of error which has been discussed above is thus without significance The ratio r is calculated for the total of 84 N and F type cells The means and standard deviations of the means for the two groups are respectively

$$r_N = 0\ 75 \pm 0\ 15, \qquad r_F = 0\ 67 \pm 0\ 13$$

Both groups of readings are with very close approximation distributed normally, and a χ^2 test shows that both groups are equally significant The t value for the two populations is 2 58, i e less than the value corresponding to the 1 % level of chance, 2 75 The difference between the N cells and the F cells can thus not be regarded as significant Furthermore, as the proportion of the F cells is 10 %, at most 20 % of the cell population, their significance for measuring inaccuracy is reduced further

It appeared reasonable to attempt to derive a more correct expression for the RNA changes per cell, by correcting for differences in cell volume due to shrinkage This correction was omitted, however, as the eccentric siting of the measuring field in the cell, together with the large numerical aperture, seems to lead to the result that a simple volume correction overcompensates the effect for very large and very small cells (This was also indicated by tentatively corrected results showing a less well defined curve with unchanged tendency)

DISCUSSION OF RESULTS

Our knowledge of the function of the first neurone in the auditory pathway derives mainly from electrophysiological recording of the reaction to sound stimulus Such a sound stimulus is most often applied in the form of impulses of millisecond duration so called clicks, but in recent years interest has been directed to the reaction of the nerve elements to prolonged stimuli By using microelectrodes a varying degree of adaptation has been demonstrated in the different fibres of the cochlear nerve at times with full adaptation occurring as late as 15 minutes after the start of the continuous sound stimulation (Rose Galambos & Hughes, 1959) Most recently Starr & Livingston (1963) by means of permanently implanted microelectrodes in cats have followed the electrophysiological phenomena along the auditory pathway during and after prolonged stimulation with white noise Animals in the normal waking state showed prolonged but decreasing inhibition of the electrophysiological response (cochlear microphonics and action potentials in the cochlear nucleus), a result of the function of the muscles of the middle ear and of central inhibiting mechanisms This inhibitory effect was completely abolished by barbiturate anaesthesia Conversely, no sign of auditory fatigue or adaptation was found The inhibitory effect of the central efferent tracts on the first neurone of the auditory pathway has been demonstrated most recently by Fex, (1962)

The present authors feel however that it is too soon to attempt to establish a correlation between the biochemical and electrophysiological reaction of the cochlear nerve to noise especially with respect to the phenomena of fatigue and adaptation

Hamberger & Hydén (1945) made a comprehensive examination of the biochemical reaction of the nerve cells of the spiral ganglion to sound stimulus They used a pure tone stimulus of 6000 c/s 80 db for a period of 15 minutes to 4 hours Following the stimulus the experimental animals were sacrificed at intervals from 0 up to 4 weeks and a determination of the extinction in the spiral ganglion cells made at 2600 Å and 2800 Å by means of UV spectrophotometry Even allowing for the difference in the sound stimulus there is a considerable discrepancy between their results and the present ones In their experiments there was no immediate change in the RNA and protein content and a fall did not take place before the lapse of 24 hours There was then a steady fall during the first week to a minimum which persisted through the second week and then a rise to normal extinction values during the third week Considerable nuclear cap formation was observed both during the fall and rise in the extinction value In contrast to these findings the present experiments showed an initial fall in extinction followed by a steady rise to normal values in the course of two weeks It seems reasonable to believe that the explanation lies in the *fact that extinction* in a UV spectrophotometer at 2600 Å represents a summation of RNA *and* protein content in the nerve cell whereas gallocyanin selectively stains RNA under pH 2

It is *unfortunately* the case that a stress which results in significantly measurable change in cell extinction can hardly avoid affecting the *functional* capacity of the end organ But studying peripheral ganglion cells by the use of specific stimuli the complementary situation to that above cannot be ignored that the functional condition of the *receptor* is *significant* for the restitution of the ganglion cell It has been demonstrated that light stimuli are necessary *for the* development of the cells in the retinal ganglion (Brattgård 1952) *The reversible* change in the outer hair cells observed in the present *experiments* and perhaps more pronounced than in the experiments of Hamberger & Hydén *who did not* take this point into consideration might well have an influence *on* the regeneration of RNA in the ganglion cells The rather quick return *of hearing* shows however that these cells can receive impulses soon after the termination of the sound stimulus The studies preceding the present *one* and using the same strong stimulus for a varying period 30 minutes *to 6 hours* appear to show that in the case of strong stimuli the receptor *organ* perhaps functions like an electric fuse by means of which the ganglion cells *are protected* Studies of the effect of acoustic trauma on the spiral *ganglion* (*Hammer* 1956) using series of revolver shots with approximately the same frequency spectrum of intensity as in the present stimulus in our view only show that no regeneration of RNA occurs when the organ of *Corti* has been completely destroyed It is

difficult to imagine that such a trauma should result in primary destruction of the ganglion cell. Studies now proceeding in the authors' laboratory, on damage to hair cells from antibiotics (Falbe-Hansen, 1963) and on hereditary, progressive degeneration of the organ of hearing in mink (Thomsen & Salomon, 1963), suggest that changes in ganglion cells are secondary to damage to hair cells, and often show a considerable time lag.

CONCLUSIONS

1. After subjecting the spiral ganglion in guinea-pigs to a powerful acoustic stress (127 db white noise for 1 hour), gallocyanin-chrome alum staining at pH 1 64 revealed an initial decline in cytoplasmic basophilia in the ganglion cells, reflecting corresponding changes in RNA content. This relative chromophobia gradually disappeared in the course of 15 days.

2. The above observation may be taken to indicate that a stimulus of this strength, which does not involve a shock wave, can be tolerated by guinea-pigs

3. It is inconceivable, therefore, that shock waves with the same frequency spectrum of intensity as the present stimulus, and which can destroy the organ of Corti, can produce direct degeneration of the ganglion cells in the spiral ganglion Such degeneration must be secondary to destruction of the organ of Corti.

ZUSAMMENFASSUNG

45 anasthesierte Meerschweinchen wurden 1 Stunden lang mit "white noise 127 db" als "free field" Stimulus behandelt 0–31 Tage nach der Stimulation wurden die Tiere seziert und auf den Grad der zytoplasmatischen Basophilie in den Spiral ganglienzellen nach Farbung mit Gallozyaninchromalaun mit einer H Ionenkonzentration von pH 1,64 als Indikator fur relative Anderungen des Ribonukleinsäure-Inhalts untersucht Ferner wurden die Ganglienzellen auf etwaige Grössenänderungen untersucht Ein initiales Gefalle in der zytoplasmatischen Basophilie wurde festgestellt, im Laufe von 2 Wochen trat eine stufenweise Ruckkehr zu den Normalwerten ein, was bei der Untersuchung von 9 Kontrolltieren ermittelt wurde Es wurde keine signifikante durch die Larmbelastung hervorgerufene Veranderung der Zellengrosse festgestellt Als Konklusion ergab sich, dass eine Larmbeeinflussung dieser Grosse von Meerschweinchen ertragen wurde, sowie dass die fruher nach Schockwellen gleicher Intensitat beobachtete Ganglienzellen-Degeneration eine im Verhaltnis zur Destruktion des Cortischen Organs sekundare Erscheinung sein muss

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PNEUMOCEPHALUS

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Pneumocephalus as a result of fistulous communications between the skull cavity and the paranasal sinuosities or the cell system of the temporal bone is described. Three different cases of the traumatic type and one case of the *postoperative form are presented.*

By pneumocephalus (p. c.) is meant an accidental, generally intracranial collection of air. Other names for this condition are intracranial pneumatocele, aerocele and pneumocranium. It was first described in an autopsy report in 1884 by Chiari and radiologically by Luckett in 1913. P. C. results from fractures which are directly penetrating the skull or which involve the paranasal sinuosities or the cellsystem of the temporal bone through which an open communication arises to the skull cavity. Exceptionally, p. c. can also result from tumours and infectious processes destructive to the bones of the cranium, in which case similar fistulous communications arise (Chiari 1884, Cushing 1930, Hamberger & Diamant 1946, Ruder 1951, Hangai 1960, Pell & Carroll 1963). Additionally, p. c. can ensue from infections with gas producing organisms (Luckett 1913) and postoperatively in connection with brain surgery. Except for the last mentioned form of p. c. the traumatic one is the most usual but is, however, considered relatively rare keeping in mind the high frequency of fractures of the actual type (Dandy 1933, Coleman 1937, Moel 1950, Lindgren 1954, Chimura & Davalli 1960).

The anatomical conditions within the actual area of the injury and the extension of the latter are determining factors for the localisation of the air. Thus the dura, the arachnoidea or the very cerebral substance can be damaged by which subdural, subarachnoid or intracerebral collection of air is contained. In the last mentioned case a perforation to the ventricular system can also happen. From a radiological point of view such a ventriculogram can also be produced by passage of the subarachnoid air into the ventricular system the normal way via Magendie's and Luschka's foramina. Extradural p. c. is, on the other hand, very rare because the dura, at least over the paranasal sinuosities, more easily ruptures than it becomes loose as the dura *here is relatively thin and firmly adherent to the underlying* bone (Moel 1950). Epidural p. c. has, however, been described by Reisinger (1919).

Even if the kind of injury decides the type of p. c. the frontal fractures *are considered to more often give subdural p. c.*

of the skull involving the posterior ethmoid cells and sphenoid sinus give a subarachnoid type (Dandy 1945 Mock 1950)

In skull injuries of the above described kinds one has to expect complications not only of the meningitis type By temporary increases of pressure in the sinuosities or cell system air can be forced into the skull cavity through the developed fistula If at the same time a valve mechanism exists the air cannot leave the skull the amount of air increases and the intracranial pressure is hereby risen Often p c appears after latent periods of varying duration In relatively complicated fractures usually the intracranial air appears within 48 hours (Lewis 1928) In Dandy s series of 24 cases there is a variation in time of one day to ten months for the occurrence of p c Garland and Mottram describe a case of p c occurring 9 weeks after the trauma and Lewis a similar case in which p c appeared after 2½ years This latency is due to the fact that the opening to the skull cavity in the beginning is blocked by blood and oedema and at the same time the patient is in an inactive state possibly unconscious and temporary extracranial increases of pressure seldom appear When blood and oedema have been absorbed the fistulous communication is open and as the patient simultaneously becomes more active (turns in bed coughs sneezes swallows etc) there are greater possibilities for more frequent increases of pressure in sinuosities and cell system Parallel to the increased pressure in the skull the condition of the patient deteriorates continuously Usually a gradual improvement follows the appearance of a liquor fistula through which an equalization of the pressure takes place

Some Different Types of p c

Case 1 (Fig 1)

A 49 year old man who in attempting to commit suicide forced a pair of scissors through the skull Radiological examination on arrival in hospital showed a bone defect 5 15 mm big in the right frontal region and air in the lateral ventricles The patient showed signs of meningitis which however departed after antibiotic therapy and the air in the ventricular system had almost completely disappeared after three weeks (A following cerebral angiography showed an arterial aneurysm the size of a pea in one of the small branches of the right middle cerebral artery Encephalography revealed a central atrophy with a leftsided predominance)

Case 2 (Fig 2)

A 46 year old man who after a car accident was found with haemorrhage from the left ear Radiological examination on the same day showed a diastasis of the lambdoid suture on the left side and a fracture of the left temporal bone passing through the densified cell system Furthermore p c existed with subdural and subarachnoid air frontally and in the basal cisterns around sella turcica The examination showed also a liquid fistula from the left ear After two weeks the patient recovered and had no signs of neurologi



Fig. 1. Case 1. Traumatic bone defect, right arrow. P.C. with air in the lateral ventricles, left arrow (supine position, horizontal beam).

cal symptoms. The flow of cerebrospinal liquid had ceased completely and the intracranial air had disappeared.

Case 3 (Fig. 3)

An 18-year-old man who was admitted to hospital after a car accident. Radiological examination on the same day revealed a fracture through the right frontal region reaching down to the partly opaque right frontal sinus, the posterior wall of which was also fractured. On the same day a bilateral trepanation was performed and a big subdural haematoma on the right side was removed. The patient, who showed signs of a serious brain contusion and amaurosis of the right eye, improved only very slowly but could be sent home after three weeks hospitalization. Six weeks after the accident, however, the condition of the patient deteriorated again and he suffered from vomiting, headache, and unconsciousness of short duration. Then his condition improved somewhat in conjunction with a discharge from his nose. He was re-admitted to hospital. He was apathetic but answered adequately to questions. In his nose was demonstrated a liquor fistula. Apart from amaurosis as before and a right-sided ptosis he had no neurological symptoms and no signs of meningitis. Radiological examination (six weeks after the trauma) showed, as before, a frontal fracture and opacified frontal sinuses in addition to large quantities of intracranial air located partly in



Fig 2 4

Fig 2 Case 2 4 Fracture from the la nb lo d suture through the partly lensif e l cell system of the left temporal bone B P C with sub lural and subarachnoidal a r (supine position horizontal beam)

large frontal cavities most likely in the frontal lobes partly subdurally subarachnoidally and intraventricularly After four weeks of intensive antibiotic therapy during which time the condition was largely unchanged the patient was operated upon again The defect between the skull cavity and the right frontal sinus was covered Large cavities in the frontal lobes were punctured Post operative radiological control a week later showed that all intracranial gas had disappeared The condition of the patient soon improved and three weeks after the operation he was almost without symptoms The liquid flow disappeared after the operation

No cases of p c involving tumours or infections have been observed by us They are probably extremely rare More or less pronounced p c after intracranial operations is on the other hand of common occurrence Usually however it disappears relatively quickly after one or two weeks but can occasionally remain for a longer time as is demonstrated by the following case

Case 3 (Fig 3)

A previously healthy 63 year old man who had suffered during the preceding two months from a state of mental confusion A doublesided carotid



Fig 2 B

angiography showed bilateral subdural haematomas with a left sided predominance The haematomas were removed by trepanation The brain showed, however, no signs of expansion during the operation, and postoperatively the condition of the patient rather deteriorated Four days after the operation the radiological examination revealed large quantities of air and fluid subdurally on both sides Repeated punctures however, resulted in a reduction of the air The condition improved successively Not until six weeks after the operation was the patient restored to health and all the air removed

DISCUSSION

Generally, cranial fractures are to be considered as serious conditions, not only with regard to the brain injuries which could be involved with a trauma against the head, but also in respect of the complications which could result from the fracture Such complications are usually haemorrhage and infection By penetrating damages or by fractures involving the paranasal sinuosities or the cell system in the temporal bone, p c can, however, also set in, a complication which can prove fatal because of an increased intracranial pressure It is of importance to note that p c does not inevitably



Fig 3 A

Fig 3 Case 3 A Fracture through the right frontal region with densified frontal sinus *B* and *C* Fracture through the posterior wall of the frontal sinus (arrow in *B*) I C with intracerebral (frontal lobes) subdural subarachnoidal and intraventricular air *B* Prone position *C* Supine position

appear immediately after the trauma (as in cases 1 and 2) but can occur after a latent period of variable duration (as in case 3) In order that intra cranial pressure should evolve there must be a valve mechanism in the fracture which permits the air to enter the skull cavity, but not to leave it

The fistulous connections to the skull cavity which are necessary for the rise of p c as well as for the liquid flow, can close up spontaneously (cases 1 and 2) otherwise this must be made operatively as in case 3

Regarding the high frequency of the here described kind of fractures the cases of p c are relatively low This can however be a deceptive pheno menon Small amounts of air can be disregarded in the acute radiological examination However if the patient is regularly examined radiologically by horizontal beam minimal amounts of air can be more easily demonstra ted Another reason for diagnostic difficulties is as described above that *p c develops after a certain period of latency The presence of a fracture* and together with this, signs of a brain contusion are clinically often re garded as sufficient to explain the condition of the patient Only a repeated radiological examination can reveal the development of p c as explanation of a slower than usual rate of recovery Repeated radiological investigations are thus of great importance in these cases in order to observe the occurrence of p c a complication of vital diagnostic significance which perhaps is not so unusual in certain types of cerebral traumas

The postoperative form of p c has another origin and is a vacuum pheno menon In the above related case 4 the brain had been compressed by double sided subdural haematomas After those had been removed the brain

Fig 3 *B*



Fig 3 *C*



Fig 4 A



Fig 4 B

Fig 4 Case 4 A and B, Postoperative p e with subdural air and liquid (supine position)

showed, however, no signs of expansion. The space left by the removal of the haematomas was displaced by gas and fluid, which were only slowly absorbed simultaneously with the expansion of the brain. There is no intracranial increase of pressure to be expected because of p. c. in such a case and consequently the occurrence of gas is not a serious symptom.

ZUSAMMENFASSUNG

Pneumocephalus als Resultat von Fistelverbindungen zwischen der Schädelkavität und den Nasennebenhöhlen bzw. dem Zellsystem des Felsenbeines wurde beschrieben. Drei verschiedene Fälle vom traumatischen Typ und ein postoperativer Fall werden gezeigt.

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BEHAVIOUR OF CYTOCHROME OXIDASE ACTIVITY IN THE COCHLEA OF THE GUINEA PIG FOLLOWING ACOUSTIC STIMULATION

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After having schematically drawn attention to the distribution of cytochrome oxidase in the cochlea of the normal guinea pig (described in a former work) and the principal data of the literature relating to the histochemical and biochemical variations shown in the inner ear subsequent to sound stimulation, the authors describe the method of the investigation and its results. Intense sound stimulation (100 decibels) with pure tones of diverse frequencies (250, 2000, 4000, 8000 Hz) for a period of 3 hours brings about a histochemically demonstrable reduction of enzymatic activity; this reduction is diffuse, does not depend on the frequency used and is apparent not only at the level of the organ of Corti but also, more especially, at the site of the stria vascularis and the external spiral sulcus. These results are then briefly commented upon.

One of the most interesting problems of cochlear biology—as pointed out by Vosteen (1960)—is the study of the sources of energy. It is a well known fact that nearly all metabolic reactions receive energy from oxidative metabolism (cellular respiration) and it is equally well known that this in its turn is strictly dependent upon the activity of the enzymatic respiratory system.

The possibility of applying a reliable histochemical technique for the study of cytochrome oxidase—namely the G Nadi reaction modified by Nachlas, Crawford, Goldstein & Seligman (1958)—to research on fresh tissues has induced us to examine the behaviour of the enzymatic activity in the acoustic receptor subsequent to stimulation by pure tones with different characteristics.

In a previous investigation we studied the cytochrome oxidase distribution histochemically in the anterior labyrinth of the normal guinea pig. The positivity to the reaction appeared particularly evident at the level of the organ of Corti (Fig. 1): when highly magnified, the granules of purple indonaphthol indicating the ferment could be localised in the cytoplasm of the internal and external ciliated cells and more precisely in the mitochondrial area (Fig. 2). The response of the supporting cells to the reaction was also positive, as too was that of the structures of the external spiral



Fig. 1. Cochlea of normal guinea pig. G. Nadi reaction (modified by Nachlas et al. 1958) for cytochrome oxidase. Fresh preparation obtained by dissection under the operating microscope.

sulcus. The cochlear area where cytochrome oxidase appeared most abundant, however, was the stria vascularis (Fig. 3). No noticeable differences were observed in the distribution of the enzyme in the various turns of the cochlea. It therefore seems evident that cytochrome oxidase is particularly active in cellular groups with high metabolic activity.

During the last ten years, experimental and clinical research into the results of various acoustic stimuli on the inner ear have been intensified. We shall, however, confine ourselves to touching only upon the more important histochemical and biochemical studies.

Experiments with radio-active phosphorus P^{32} (Bydll & Krejci 1951) have shown that the value of the "turn over" for the organ of Corti and the spiral ganglion are lower after stimulation by sound.

Similarly, a marked inhibitory effect of acoustic stimulation on the metabolism of amino acids and proteins of the inner ear has been observed (Ito 1954, Mizukoshi *et al.* 1958).

It has also on more than one occasion been shown (Hammer 1956



FIG 2 Highly magnified detail (× 2500) of the organ of Corti of a normal guinea pig at the level of the basal turn

Katagiri & Ohashi 1959) that there is a reduction in the content of nucleinic acids and in the concentration of plasmatic proteins in the cells of the spiral ganglion in the external acoustic cells and in the stria vascularis after the *animals have been exposed to sounds of any kind whatsoever*

Zorzoli & Boriani (1958) drew attention to a diminution of glycogen in the sensory cells after stimulation by sounds of average intensity (50 decibels) and short duration (30 minutes) More prolonged excitation or with sounds of greater intensity resulted in the disappearance of the histochemically identifiable glycogen

Vosteen (1958 1960) observed after acoustic stimulation of considerable duration a diminution in the *activity of succinodehydrogenase* in the cochlear nerve endings and in all the external ciliated cells even before any



FIG 3 Cochlea of normal guinea pig Fragment of the spiral ligament with the stria vascularis (taken from the basal turn) × 190

structural or histological damage became apparent No obvious alterations could be seen in the internal acoustic cells

Vinnikov & Titova (1958) described the results of stimulation by bell ringing for the duration of one hour in experiments on the guinea pig and the rabbit this brought about a reduction in the activity of succinodehydrogenase and cytochrome oxidase in the external ciliated cells and the spiral ganglion High frequencies caused the greatest modifications in the lower spirals whereas the effects of low frequencies were apparent in the upper turns

These same authors subsequently made an extensive histochemical study (1963) of the distribution in the organ of Corti—and the modifications induced by acoustic stimulation—of numerous enzymes (acetylcholine esterase phosphorylase succinodehydrogenase cytochrome oxidase phosphatase) as well as of glycogen and the proteins and the functional groups –SH –SS– –COOH

Del Bo & Ottaviani (1960) have demonstrated—also in the guinea pig—that pure tone sound stimulation causes a reduction in succinodehydrogenase in a similar manner with different frequencies this reduction is mainly related to the time of exposure to the sound and involves not only the specific sensory cells but also elements of the stria vascularis and the spiral limbus

Engstrom & Ades (1960) have carried out an original type of investigation into the effect of pure tones of high intensity (150 decibels for different lengths of time) and of noises caused by jet aeroplane engines helicopters etc on the sensory epithelium of experimental animals *The cochlea* when examined under the electronic microscope showed structural alterations in the sensory supporting and ganglion cells and at the nerve endings The nuclei of the ciliated cells tended to swell the chromatin was irregularly distributed and nucleoli were approaching nearer to the nuclear membrane After lengthy exposure the mitochondria of the cells lost their lamellar or membranous structure tending to swell and to degenerate

Koide *et al* (1960) drew attention to a diminution of the oxygen pressure in the inner ear of animals subjected to intensive stimuli an increase in the *concentration of glucose in the perilymph morphological alterations* of the mitochondria of the apex as being the first modifications caused by the sounds on the external ciliated cells

In a previous investigation (Conti 1961) a histochemical study was carried out concerning the modifications induced by acoustic stimuli of high intensity (90 decibels) and long duration (3 hours) on the distribution of acetylcholine esterase in the cochlea of the guinea pig With tones of a frequency of 250 Hz the disappearance of the precipitate indicative of enzymatic activity in the apical turn was observed whereas with sounds of 2000 Hz the reduction was more marked at the level of the superior medial spiral More acute tones (4000 to 8000 Hz) brought about a definite decrease in the precipitate especially at the site of the medial and inferior turns respectively The diminution in the positivity of the reaction was more marked at the level of the external ciliated cells

METHOD

In view of the lability of the respiratory enzymes the reaction could only be produced on fresh non fixed tissues

The investigation was carried out on young guinea pigs exempt from any disease of the ear In the cabin of the G 5 Amplifon audiological unit 20 animals were subjected to a stimulus represented by the sound produced by a model 813 EI IT audiometer suitably amplified and transmitted to a loud speaker placed in contact with the cage containing 2 guinea pigs at a time The characteristics of the sound were as follows intensity 100 decibels frequencies 250 2000 4000 8000 Hz for the duration of 3 hours without interruption The animals were slaughtered in the same sound proof chamber in order that the sound stimulus should not be interrupted until the very last moment of life

The reaction was effected on fresh tissues cut off from the cochlea under the dissecting microscope

The G Nadi method modified by Nachlas Crawford Goldstein & Selig man (1958) enables the cytochrome oxidase activity to be shown histo chemically in the form of small accurately localised granules of purple indonaphthol as a result of the reaction between alpha naphthol and 4 amino N N dimethylnaphthylamine in the presence of the enzyme

The method followed by us was described in a previous work—*on the* distribution of cytochrome oxidase activity in the cochlea of the normal animal—to which we refer the reader (Conti & Borgo in the press for pub lication in *Laryngoscope*)

In order to substantiate the specificity of the method the control prepara tions were treated similarly to the principal reaction (also on small slices of cardiac muscle cut by the freezing microtome) by means of

1 fixation in formalin for approximately 1 hour

2 incubation in the medium solution with the addition of KCN 10^{-3} M specific inhibitor of cytochrome oxidase

No trace of pigment can be discerned in the usual localisations in these preparations

RESULTS

A preliminary series of experiments with stimuli of low intensity (40 decibels) and of different frequencies (250 1000 and 4000 Hz) even if prolonged up to 3 hours did not make any notable variations evident in so far as the distribution of cytochrome oxidase in the animal under normal conditions was concerned

When however the intensity of sound was increased to 100 decibels always for 3 hours duration the modifications observed histochemically were constant and significant

In fact in all the cochleae examined a reduction in the enzymatic activity was evident this reduction was diffuse and extended uniformly to all the

structural or histological damage became apparent. *No obvious alterations* could be seen in the internal acoustic cells.

Vinnikov & Titova (1958) described the results of stimulation by bell ringing for the duration of one hour in experiments on the guinea pig and the rabbit: this brought about a reduction in the activity of succinodehydrogenase and cytochrome oxidase in the external ciliated cells and the spiral ganglion. High frequencies caused the greatest modifications in the lower spiral, whereas the effects of low frequencies were apparent in the upper turns.

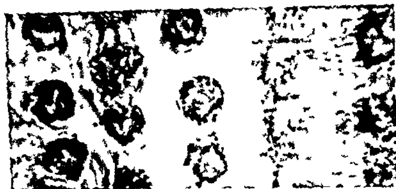
These same authors subsequently made an extensive histochemical study (1963) of the distribution in the organ of Corti—and the modifications induced by acoustic stimulation—of numerous enzymes (acetylcholine esterase, *phosphorylase*, *succinodehydrogenase*, *cytochrome oxidase*, *phosphatase*), as well as of glycogen and the proteins and the functional groups —SH, —SS, —COOH.

Del Bo & Ottaviani (1960) have demonstrated—also in the guinea pig—that pure tone sound stimulation causes a reduction in succinodehydrogenase in a similar manner with different frequencies; this reduction is mainly related to the time of exposure to the sound and involves not only the specific sensory cells but also elements of the stria vascularis and the spiral limbus.

Engstrom & Ades (1960) have carried out an original type of investigation into the effect of pure tones of high intensity (130 decibels for different lengths of time) and of noises caused by jet aeroplane engines, helicopters, etc., *on the sensory epithelium of experimental animals. The cochleae,* when examined under the electronic microscope, showed structural alterations in the sensory, supporting and ganglion cells, and at the nerve endings. The nuclei of the ciliated cells tended to swell, the chromatin was irregularly distributed, and nucleoli were approaching nearer to the nuclear membrane. After lengthy exposure the mitochondria of the cells lost their lamellar or membranous structure, tending to swell and to degenerate.

Koide *et al.* (1960) drew attention to a diminution of the oxygen pressure in the inner ear of animals subjected to intensive stimuli, an increase in the concentration of glucose in the perilymph, morphological alterations of the mitochondria of the apex, as being the first modifications caused by the sounds on the external ciliated cells.

In a previous investigation (Conti, 1961), a histochemical study was carried out concerning the modifications induced by acoustic stimuli of high intensity (90 decibels) and long duration (3 hours) on the distribution of acetylcholine esterase in the cochlea of the guinea pig. With tones of a frequency of 250 Hz, the disappearance of the precipitate indicative of enzymatic activity *in the apical turn was observed,* whereas with sounds of 2000 Hz the reduction was more marked at the level of the superior medial spiral. More acute tones (4000 to 8000 Hz) brought about a definite decrease in the precipitate, *especially at the site of the medial and inferior turns* respectively. The diminution in the positivity of the reaction was more marked at the level of the external ciliated cells.



1 Highly magnified detail (× 2800) of the organ of Corti of guinea pig stimulated for 3 hours with the sound of 4000 Hz at 100 decibels (at the level of the basal turn) Compare Fig 2 The enzymatic activity at the site of the external ciliated cells appears moderately reduced

It is thought that the structural integrity of the mitochondria denotes the normality of the activity of the enzymatic compounds which they contain and particularly of the *respiratory chain* The fact that Koide *et al* (1960) and Spoendlin (1958) have described—as being the first *consequences* of sound stimulation—structural alterations (swelling greater transparency) of the mitochondria of the external *ciliated cells* *is also* an indication of functional anomalies of the enzymatic systems referred to and this would appear to be confirmed by our results



Fig 4 Cochlea of guinea pig stimulated *with the* sound of 1000 Hz *at 100* decibels for 3 hours fragment of spiral ligament with stria vascularis (taken from the basal turn) × 300 Compare Fig 3 A pronounced reduction in the cytochrome oxidase activity is evident



Fig. 4. Cochlea of guinea pig after stimulation for 3 hours with sounds of 1000 Hz at 100 decibels. Enlarged 12 times. Compare Fig. 1. A certain diminution in positivity for cytochrome oxidase is apparent.

cochlear turns, independently of the frequencies used, viz. 250, 2000, 4000 and 8000 Hz (Fig. 4).

The enzymatic deficit was evident not only at the level of the ciliated cells (Fig. 5), but was particularly so at the site of the external spiral sulcus and of the stria vascularis (Fig. 6).

The presence of the pigment in the stria vascularis did not prevent the reading of the preparations, as it is well known (Beck, 1961) that it is in no way affected by acoustic stimulation.

The comparison between the normal preparations and those obtained after stimulation was obviously made with homologous preparations; in particular, the incubation time (40 minutes, at room temperature) was maintained strictly constant.

We have seen that intense and prolonged sound stimuli with pure tones of various frequencies lead to a reduction in positivity; such reduction, extended to all the cochlea turns which do not appear to be related in a significant way to the frequencies employed, is demonstrable—even though to a limited extent—at the level of the acoustic cells, but also especially at the level of the stria vascularis and the spiral prominence.

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Various types and degrees of biochemical and histochemical modifications after sound stimulation have been described according to Koide (1958) however they are for the most part attributable to an alteration of the energetic basal system this may be caused (1) by lesion or mechanical destruction of the respiratory chain in the mitochondria (which the experiments of Hogeboom & Schneider 1952 may support) or (2) by hypoxia

The latter hypothesis is upheld by the observations of Vosteen (1958) according to which succinodehydrogenase disappears from the organ of Corti after sufficient acoustic excitation whereas anoxia accentuates this histochemical modification and from the findings of Koide *et al* (1958) and Misrahy *et al* (1958) the oxygen pressure is reduced in the inner ear after exposure to intense sounds It would seem therefore that hypoxia is one of the most important factors in the determination of damage from acoustic trauma

In accordance with this theory our investigations which after sound stimulation revealed a reduction in cytochrome oxidase activity (as well as in that of dehydrogenase—Del Bo & Ottaviani Vosteen *et al*) besides denoting mitochondrial alterations with definite metabolic disorder (inhibition exhaustion of the enzyme or of metabolites?) show a certain functional correlation between the specific sensory elements (ciliated cells) and the structures whose function it is to regulate the endolymphatic metabolism (stria vascularis external spiral sulcus)

ZUSAMMENFASSUNG

Nach einer schematischen Beschreibung der Verteilung der Cytochromooxydase in der Schnecke des normalen Meerschweinchens die in einer früheren Arbeit erläutert worden war sowie der wichtigsten im Schrifttum niedergelegten Tatsachen betreffs der histochemischen und biochemischen Veränderungen die am inneren Ohr nach Schallreizen festgestellt wurden erklären die Verfasser die Methode und die Ergebnisse ihrer Studien Eine starke Schallreizung (100 dB) mit reinen Tönen verschiedener Frequenz (250 2000 4000 und 8000 Hz) während 3 Stunden ruft eine histochemisch beweisbare Verringerung der Enzymtätigkeit hervor diese Herabsetzung ist ausgedehnt hat keine Beziehung zur angewandten Frequenz und ist nicht nur am Cortischen Organ nachweisbar sondern auch und besonders an der Stria vascularis und dem Sulcus spiralis externus Diese Ergebnisse werden dann kurz besprochen

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EXPERIMENTAL STUDIES ON VESTIBULAR MECHANISMS

II VESTIBULAR DISORDERS IN DECORTICATED CATS

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The effect of the removal of the neocortex upon vestibular reflexes was observed in a series of ten cats The behavior postural reflexes and motor performances of these animals fitted the classical description of the decorticated cat No spontaneous nystagmus was ever observed but it was possible to provoke it by repetitive vestibular stimulation Transitory positional nystagmus of both irregular and direction changing types were seen for several days in a few cases The responses of both normal and decorticated cats to caloric and rotatory stimulation exhibited qualitatively a remarkable similarity Quantitatively however there were some differences between the two sets of responses After total ablation of the neocortex the passive optokinetic nystagmus was demonstrated in a few cases

It is known that the cerebral cortex is not essential for eliciting vestibular reflexes Rotatory and caloric vestibular reactions tonic labyrinthine reflexes and labyrinthine righting reflexes have been demonstrated in thalamic or mid brain preparations (Bauer & Leidler 1912 Magnus 1924 Rademaker 1931) In man de Kleyn & Schenk (1931) evoked vestibular nystagmus in a child without cerebral hemispheres cerebellum and motor centers of the third and fourth cranial nerves The histological examination showed that only the nucleus of both sixth nerves and both abducens extraocular muscles were present

These classical studies in decortication provided a substantial amount of information for setting the physiological basis of posture and eye movements elicited by vestibular stimulation However the vestibular disturbances which may be associated with the removal of the neocortex have been somewhat neglected

The purpose of this work was to observe the vestibular signs which might be associated with the ablation of the cortex in the cat The study may help to increase the understanding of vestibular disorders observed in humans with diseases of the central nervous system

METHODS

The observations were made in ten adult cats which survived the ablation of the neocortex In the early stages of this series four animals died because

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of problems associated with the surgical procedure such as hemorrhages and accidents of anesthesia. Behavior, postural reflexes, locomotion, vestibular disorders and vestibular function of all of the animals were examined before and after decortication. The details regarding surgical procedure for ablation of the neocortex and methods for eliciting and recording nystagmus are described elsewhere (Fernandez & Schmidt 1962).

The cats were sacrificed at various intervals between fifteen and forty days after decortication. The brain and temporal bones were removed and prepared for microscopic studies. The gross pathological and microscopic findings have been summarized in a previous report (Fernandez & Schmidt 1962).

RESULTS

Adequate nursing and thorough cleaning of the cats and their cages permitted maintenance of healthy animals until the experiment was discontinued at about two months. Some ate spontaneously when the mouth was in contact with or near food, but no signs of food recognition or excitement during feeding hours were ever observed.

The pupillary reactions were active and consensual. There was no paralysis of extrinsic ocular muscles. Noxious stimuli, strong noises and even mild disturbances produced avoidance and/or released the classical sham rage reaction described originally by Goltz (1892).

Usually the Preyer's reflex could be elicited and some animals even exhibited signs of sound localization. The reaction may represent an exaggerated Preyer's reflex as one more manifestation of the release of the subcortical center from higher inhibitory influences.

The observations on postural reflexes and locomotion fitted the classical description of decorticated cats (Magnus 1924, Ranson & McNattin 1930, Rademaker 1931). The animals exhibited all the components of the complete act of walking, that is, rhythmic movements of fore and hind legs, postural reflexes, equilibration and ability to maintain upright posture.

Progression reactions, tonic labyrinthine reflexes and righting reflexes were present. However, the righting reflex during the free fall was consistently absent in all animals. In the standing position, abnormal posture of legs, such as crossing or abduction, occasionally occurred. While walking and in crouching, sitting or standing position, the animals presented an apparently natural distribution of postural tone (Fig. 1 A). When suspended, however, a strong persistent extensor rigidity of the limbs, head and tail was assumed (Fig. 1 B). This hypertension disappeared as soon as the feet made contact with the ground.

A. *Spontaneous, Provoked and Positional Nystagmus*

Spontaneous nystagmus was not observed in our series, but it could be provoked by *repetitive* caloric stimulation. The disorder, appearing a few seconds after completion of the caloric response, consisted in a transitory



Fig 1 Cat I-68 on the fifteenth day after ablation of neocortex In *A*, the animal is in a sitting position showing a normal distribution of tonus In *B*, suspension was followed by pronounced extensor rigidity of neck extremities and tail

spontaneous nystagmus which sometimes presented paroxysmal bouts As the caloric tests were repeated, the duration of the provoked nystagmus increased, sometimes from several seconds to several minutes The pattern of the disturbance often changed from test to test and from one animal to another

The disturbance was clear cut in four out of the ten cats of our series A case illustrating one pattern of this disorder is presented in Fig 2 The data revealed that after removal of the neocortex, this animal had no spontaneous or positional nystagmus On the sixteenth postoperative day the right ear was irrigated with water at 20°C for forty seconds The test was repeated at intervals of between five and ten minutes Provoked nystagmus appeared at the eighth caloric test and became more prominent as the tests

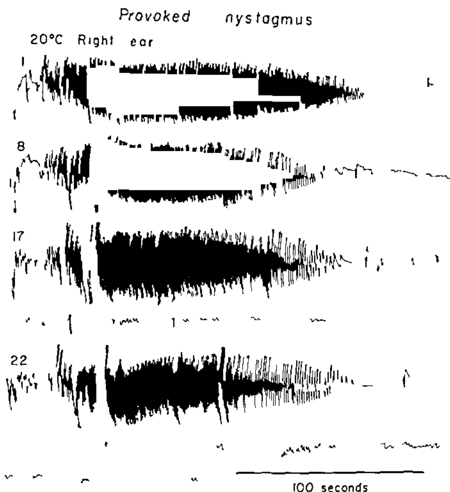


FIG 2 Provoked nystagmus recorded in decorticated cat C 41 This animal received a trial of [illegible] irrigations of the right ear with water at 20°C The responses to irrigations 1, 8, 17 and 22 are depicted in this figure The provoked nystagmus appeared at the eighth caloric test and became more and more pronounced as the tests were repeated Consistently there is a latency between response to caloric stimulation and provoked nystagmus The direction of the latter is opposite to that of the former

were repeated In the twenty second test the duration of the disorder was six minutes The follow up showed that no spontaneous or positional nystagmus occurred on the following days

The procedure repeated eighteen days later again showed a provoked nystagmus which built up with repetition of the tests A third trial done three days later produced similar results The last two tests of this trial consisting of 34 caloric tests are presented in Figure 3 The figure illustrates the point that the provoked nystagmus is unidirectional regardless of the reaction elicited by caloric stimulation In this case the provoked nystagmus was toward the right with the irrigation of either left or right ear with water at 20°C

Transitory positional nystagmus of the direction changing type as defined by Nylen (1950) *was seen in three cases for several days Usually the* nystagmus was of small amplitude, low frequency and rhythmic The fact

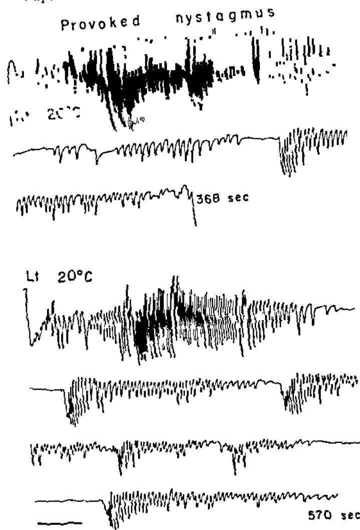


FIG 3 Provoked nystagmus recorded in decorticated *cat I-11* *Calorization* of right ear with water at 20 C produced nystagmus to the left *which lasted* 140 seconds After a latency of 23 seconds a provoked nystagmus to the right appeared for 105 additional seconds Calorization of the left ear with water at 20 C produced nystagmus *to the* right for 135 seconds After a latency of 25 seconds a provoked nystagmus to the right was *recorded* for 310 additional seconds Notice the paroxysmal character of the provoked nystagmus *Time marker* is 20 seconds

that positional nystagmus occurred in only a few cases suggests it may represent an anatomical and/or functional change in the vestibular system, associated with the surgical damage

Commentary

The *term* "provoked nystagmus" as used *in* this report was adopted because its pattern can be compared with the pattern of the "provoked nystagmus" seen in man (Frenzel, 1955, Stenger, 1955, Aschan & Stable,

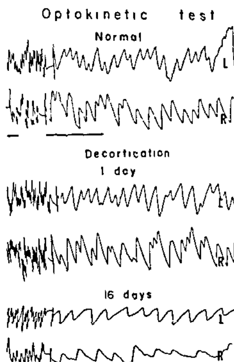


FIG 4 Cat F 55 Optokinetic nystagmus to the left (*L*) and right (*R*) before and after decortication Notice that the nystagmus wave form following decortication is similar to that preceding ablation of the neocortex The time markers represent a period of five seconds for both slow and fast speeds of the paper

1956) This term indicates a nystagmus which appears after repetitive positional tests or complete oto-neurological examinations It can be either a spontaneous nystagmus or a positional nystagmus, usually of Type II, or a change of one into the other Frenzel (1955) proposed that the 'provoked nystagmus' may be due to a decrease in threshold to vestibular stimulation after repetitive positional or other vestibular tests

Our data showed that the disturbance is associated with repetition of the stimulus it appears after the normal response to the stimulus is over, it is unidirectional and transitory One mechanism which may explain the disturbance is the so called phenomenon of post tetanic potentiation, which can be observed in either monosynaptic or polysynaptic reflexes It consists of an increase in responsiveness to a test signal after a certain period of repetitive orthodromic activation It has been proposed that the nature of the mechanism underlying post tetanic potentiation may be due to structural changes in the synapses or to functional activity of reverberating circuits (Lloyd, 1949 Eccles, 1953 Malcolm, 1953)

If it is assumed that ablation of the neocortex releases the vestibular centers from the cortical sensory control, then it is possible that repetitive vestibular stimulation may potentiate the numerous synaptic relays forming the vestibulo ocular reflex arc The provoked nystagmus might be a sign of potentiation brought about by the release of vestibular centers from cerebral



Fig. 5. Dorsal and ventral views of the brain of cat E 55. The neocortex including the rhinencephalon of the right side was totally removed. Basal ganglia were destroyed. Extensive damage was found in diencephalic structures. Dilatation of third ventricle and cystic formation were found. (From Fernández & Schmidt.)

inhibition. The disturbance is not exclusively caused by bilateral ablation of neocortex, since we have observed it in animals with partial cortical damage and with lesions of posterior fossa. However, the numerous structures encroached upon the lesion impeded the correlation between provoked nystagmus and histopathological damage.

It is possible that other neural mechanisms underlie the provoked nystagmus seen in both cat and man. Perhaps the nature of the mechanism differs considerably between the two species.

B. *Optokinetic Nystagmus*

The normal cat of our series responded readily to the optokinetic test. After decortication, some presented either a few jerks at irregular intervals or no response, while others exhibited responses to both clockwise and counterclockwise optokinetic stimuli. The failure of some animals to demonstrate optokinetic nystagmus may be associated with surgical interruption or subsequent degeneration of essential subcortical pathways. A case illustrating optokinetic responses before and after removal of the cortex is presented in Fig. 4. The responses following the ablation were similar to those seen in the normal animal. The follow up, however, demonstrated a progressive deterioration of optokinetic responses. In this cat, the ablation involved

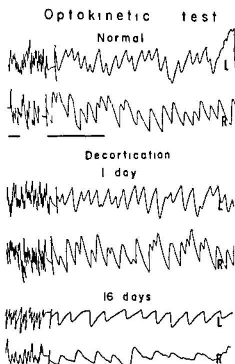


FIG. 4. Cat F 55. Optokinetic nystagmus to the left (*L*) and right (*R*) before and after decortication. Notice that the nystagmus wave form following decortication is similar to that preceding ablation of the neocortex. The time markers represent a period of five seconds for both slow and fast speeds of the paper.

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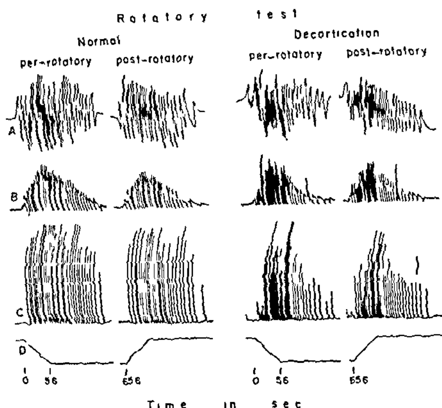


Fig. 5. Cat N 1158. Nystagmic responses to rotatory stimulation before and after removal of neocortex. *Row A corresponds* to regular nystagmus, *B* to velocity of the slow component, C to velocity *of the fast component* and *D* to angular velocity of the rotating device. The device was accelerated until it reached an angular *velocity of 120 deg/sec*, which was maintained for 61 additional seconds and then decelerated to a *standstill*. *Notice that the* pattern of the nystagmic response after removal of neocortex is similar to that *of normal* animal.

the optokinetic nystagmus is essentially a cortical phenomenon. But there is still the *question* of the *mechanism* underlying the reappearance of responses after eight to nine months.

The pathways mediating the optokinetic nystagmus have not been determined anatomically. *The data* (for references see Crosby, Humphrey & Lauer 1962) *indicate* that the visual pathways to area 18 and 19 and the pathways from these areas *back to the nuclei* of extraocular muscles are essential for eliciting *optokinetic* nystagmus *in man*. *The* passive nystagmus seems to be mediated through subcortical visual pathways to the superior colliculus and from these through the medial longitudinal fasciculus to the motor centers of *extraocular muscles* (Ter Braak 1936, Scala & Spiegel 1938). The question whether *the* vestibular nuclei may play a role in both cortical and subcortical *optokinetic* nystagmus is debatable. Ohm (1936) and Scala & Spiegel (1938) favored the hypothesis that the vestibular nuclei

extensive regions of the diencephalic structures and right pyriform area (Fig. 5). The mesencephalic structures apparently were not damaged.

Commentary

The anatomical pathways of the *optokinetic nystagmus are only* partially known and the neural mechanism underlying it is poorly understood (Cords, 1926, Fox & Holmes, 1926, Ter Braak, 1936, Scala & Spiegel, 1938, Smith & Bridgman, 1943, Carmichael, Dix & Hallpike, 1954). A point of major controversy and contradictory statements is whether the reflex is mediated by cortical and/or subcortical mechanisms. The former requires the subject's attention and fixation of gaze upon an isolated pattern moving in the visual field. This response, considered as a cortical reaction to retinal stimuli, is called the active or "look" nystagmus. This disappears after ablation of the neocortex. The nystagmus produced by a subcortical mechanism independent of the cortex is called the passive or "staring" nystagmus. It is *elicited by moving compound patterns or the whole visual field*, instead of isolated patterns. The passive nystagmus has been observed in decorticated animals (see Fig. 4), newborns, idiots and unconscious patients.

Some of the confusion and debate on this matter is caused by the generalization of results from one species to another and by the fact that different results have been reported in the same species. For instance, Ter Braak (1936), Scala & Spiegel (1938), and others supported the opinion that both cortical and subcortical optokinetic nystagmus can be elicited in man, monkey and dog. On the other hand, Bielschowsky (1938) and Cogan (1956) considered erroneous the hypothesis that in man the optokinetic nystagmus can be elicited by a subcortical reflex arc independent of the cortex. According to Cogan (1956) the difference between man and animals regarding functional localization of visual centers is a strong argument against the hypothesis of the subcortical reflex arc in man. The subprimate animals *exhibit considerable visual discrimination in the tectal regions*, which is not the case in man (Smith & Bridgman, 1943, Marquis, 1935). Consequently, in the subprimate optokinetic nystagmus may persist and it does (see Fig. 3) after removal of the neocortex. *Our data support the hypothesis* that some subprimates may be provided with a cortical mechanism, in addition to the subcortical reflex arc (Ter Braak, 1936, Scala & Spiegel, 1938, Rademaker & Ter Braak, 1948, Smith & Warkentin, 1937, and others). Apparently, the optokinetic nystagmus in the guinea pig and rabbit is mediated only by the subcortical reflex arc (Scala & Spiegel, 1938).

In primates, contradictory experimental results have been reported. Cortical and subcortical optokinetic nystagmus were observed by several investigators (Cords, 1926, Ter Braak, 1936, Rademaker & Ter Braak, 1948). On the other hand, Pasik *et al.* (1959) found that in the monkey (*M. mulatta* and *M. cynomolgus*), bilateral ablation of the entire striated cortex was associated with an irresponsive optokinetic test for a period of eight to nine months. The results strongly suggested that in these species

complex system of controlling eye movements associated with encephalization

C. *Nystagmic Response to Vestibular Stimulation*

All decorticated cats of our series exhibited nystagmic reaction to vestibular stimulation (rotatory or caloric) but the responses varied from one animal to another and in the same animal the response was often different from day to day. The pattern of primary and secondary nystagmic response to rotatory stimulation was similar but not identical to that of normal animals.

A case illustrating the pattern of responses before and after removal of the neocortex is shown in Fig. 6. The pattern is qualitatively similar in both conditions. The study of histological sections revealed a complete ablation of the neocortex and partial damage to pyriform areas and olfactory tracts. The basal ganglia cannot be identified. An extensive degenerative process extends down to the level of lateral geniculate bodies (Fig. 7).

The responses elicited by caloric stimulation were also similar to those of normal animals, although quantitative differences could be found. In a few animals the caloric nystagmus was dysrhythmic, however this abnormality was not consistently found in consecutive examinations.

Commentary

These observations emphasize the findings of Bauer & Leidler (1911) and de Kleyn & Schenk (1931) demonstrating that the neocortex is not essential for eliciting vestibular nystagmus with both slow and fast components. There is a remarkable qualitative similarity in the nystagmic reaction between normal and decorticated preparations, although quantitative differences may be found. Even the cat with complete ablation of the neocortex and extensive damage of midbrain structures exhibits vestibular nystagmus with fast and slow components. This is not surprising since the locus of the neural mechanism underlying the rhythm of nystagmus is probably placed in the vestibular centers, the vestibular nuclei (Spiegel & Price 1939) and/or the reticular formation of the medulla and pons (Lorente de Nó 1933). On the other hand it is surprising to find that ablation of the neocortex is associated with little or no alteration in duration, rhythm, direction and other parameters of nystagmus elicited by rotatory or caloric stimulation.

ZUSAMMENFASSUNG

Der Einfluss der Neocortexbeseitigung auf die vestibularen Reflexe ist in einer Reihe von zehn Katzen beobachtet worden. Das Benehmen, die Stellungsreflexe und die Motorverrichtungen dieser Tiere passten zur klassischen Darstellung der grosshirnlosen Katze. Kein spontanes Augenzittern ist je beobachtet worden, sondern es war möglich, das spontane Augenzittern durch sich wiederholende Reize herbeizuführen. Beide Typen des vorubergehenden Stellungsnystagmus, die regelwidrigen und die veranderlichen Richtungen, sind mehrere Tagelang in wenigen Fälle gesehen worden. Die Reaktionen der normalen und gehirnrindelosen Katzen

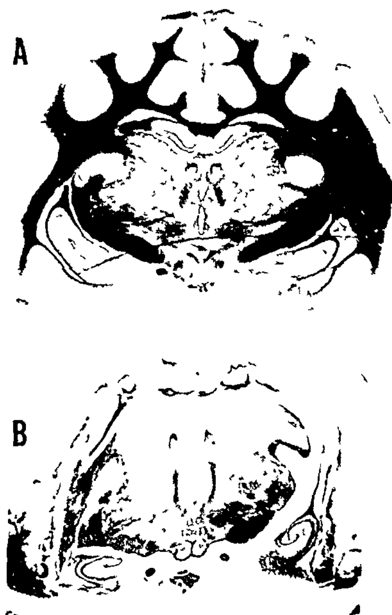


Fig. 7. Sections passing through level of medial geniculate bodies. *A* control animal. *B* decorticated (cat N 1158). The ablation of the neocortex was complete. Some remnants of the hypocampus are seen.

form part of its neural mechanism, while Dix, Hallpike & Harrison (1949) maintained that the vestibular nuclei do not participate in it. According to Lorente de Nó & Berens (1959) connections to the reticular formation must be included for maintenance of both active and passive optokinetic nystagmus.

The nature and functional significance of the dual mechanism observed in some subprimates is obscure. Perhaps the passive optokinetic may represent an old phylogenetic function which has been overcome by a more

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auf kalorische und abwechselnde Reize zeigten qualitativ eine bemerkenswerte Ähnlichkeit. Quantitativ jedoch gab es einige Unterschiede zwischen den beiden Sätzen der Reaktionen.

Nach der Exstirpation des Neocortex ist das passive optokinetische Augenzittern in wenigen Fällen gezeigt worden.

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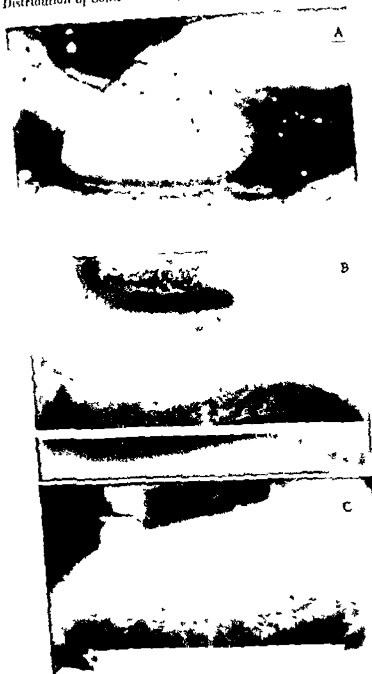
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...from the animal which was ... two hours at 37° C prior to the staining. The staining was carried out by the ...e method. The entire portions of the tissue were diffusely *stained*. *C*: The specimen was ...red by the freezing method. The staining was successful in the entire portions of the tissue

DISTRIBUTION OF SOME OXIDIZING ENZYMES IN THE COCHLEA

YASUSHI KOIDE, REIKO HANDO and YOSHIO YOSHIKAWA
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The cochlear specimens prepared by the freezing method may be subjected successfully to the precise histochemical examination on the distribution of succinic dehydrogenase and/or DPN-diaphorase The following results were obtained by this method

1 Concentration of both enzymes of both the stria vascularis and lower portions of the spiral ligament is larger in the lower turns than in the higher turns

2 There are no differences in the enzymic activities of the organ of Corti between each turn

The existence of oxidizing enzymes in the cochlea has been reported by many investigators But the distribution of the enzymes seems not to be studied well In the present paper the technical problems of staining the stria vascularis were described and the differences in enzymic activities of some cochlear tissues between each turn were presented

The Technical Problems of Staining the Stria Vascularis

It was reported that, if the cochlea was stained by the routine tetrazolium method for succinic dehydrogenase, staining the stria vascularis might not be visualized entirely satisfactorily (Koide *et al*, 1962) Thus it became necessary to clarify whether there are any failures in the technical manipulations as the cause of irregular staining of the tissue Otherwise any results obtained may be misleading in terms of normal cell physiology The staining depends on (*a*) the diffusion of the reagents into the tissue (*b*) the contents of the enzyme In this process two possibilities of error arise—diffusion of the enzyme and diffusion of the reaction product First the pathways of the reagents into the stria vascularis were examined

The inner ears were removed from adult albino guinea pigs Then the bony capsules of the cochlea with the stria vascularis and spiral ligament were taken out from the inner ear by means of a small knife It is preferable to examine the big specimen Otherwise it may be difficult to obtain precise findings

Reagents 0 2 % neotetrazolium chloride (Kanto Chemicals Co, Ltd, Tokyo), 0 1 M sodium succinate, 0 1 M sodium phosphate buffer (pH 7 4) Equal volumes of them were mixed prior to staining

Although the reagents do not reach the stria vascularis from the lymphatic space through the endolymphatic surface of the tissue, this barrier seems to be destroyed about two hours after death of the animal permitting free pass of the reagents through it When the stria vascularis exposed to post mortem changes was incubated in a solution of the reagents the red coloration diffusely began in the entire portions of the tissue (Fig 1) Further similar findings may be obtained if the cochlea was frozen by solid carbondioxide prior to staining (Fig 1)

In conclusion the existence of the barrier between the lymphatic space and stria vascularis interferes obtaining precise pattern of distribution of the enzyme in the stria vascularis Therefore if one would intend to observe the stria vascularis histochemically the freezing method (Koide *et al*, 1962) seems to be preferable

Differences in Enzymic Activities Between Each Turn

The cochleas were removed from the temporal bone of the guinea pigs and frozen by solid carbondioxide One side of the cochlea was chipped off by means of a freezing microtome and turned upside down The opposite side of the cochlea also was chipped off and the frozen specimen about 1–2 mm thick was obtained The specimens were anaerobically incubated in a solution of the reagents for succinic dehydrogenase and/or DPN diaphorase at 37°C for the time to attain an appropriate coloration

The reagents for DPN diaphorase were as follows

1 M	sodium malate	3 ml
	DPN	10 mg
1 M	sodium glutamate	5 ml
0 03 M	sodium cyanide	5 ml
0 2 %	neotetrazolium chloride	3 5 ml
0 1 M	phosphate buffer (pH 7 4)	14 ml
	ad aq dest	30 ml

1 *The stria vascularis*

First the contents of succinic dehydrogenase and or DPN diaphorase were compared between the stria vascularis *of each turn* As deep coloration due to prolonged time of incubation may interfere the precise comparison of color intensity the time *of incubation* should be controlled under a light microscope to attain an appropriate coloration

In every specimen the development of the color in the stria vascularis was very rapid in the lower *turn* as compared with that in the middle and higher turns (Figs 3 and 4) For example when the specimens were treated with the reagents for *succinic* dehydrogenase the distinct pink color became visible in the stria vascularis of *the basal turn* within few minutes of incubation and the coloration occurred in the middle turns after 5 7 minutes of incubation But the *development* of color was very slow in the higher turns especially in the apical turn



Fig. 2. The specimen was prepared by the routine method for succinic dehydrogenase. The lower and upper portions of the stria vascularis are stained darker.

The specimens were anaerobically incubated in a buffered solution of the reagents for one hour at 37°C. After a rinsing with water, they were treated with 10% formalin and examined under a light microscope.

The red color due to the formation of formazan appeared in the spiral ligament, especially in its lower portion. The reagents passed into the stria vascularis from its bilateral cut ends, showing the distinct red color in these portions, while the middle portion of the tissue remained colorless (Fig. 1). Therefore it may be concluded that the endolymphatic surface of the stria vascularis is impermeable to some components of the solution.

The color might sometimes appear in the upper and lower portions of the stria vascularis after prolonged incubation of the specimens when they were prepared by the routine method (Fig. 2). This finding suggests that the reagents may be diffusible from the spiral ligament into the stria vascularis. On the basis of the findings described above, there are two possible pathways of the reagents from the lymphatic space into the stria vascularis. One is the damaged surface of the stria vascularis, another the way via the spiral ligament. Under these circumstances the diffusion of the reagents from the lymphatic space into the stria vascularis may be very variable, depending on the local status of the tissue, and would produce very irregular development of color in the tissue.

Although the reagents do not reach the stria vascularis from the lymphatic space through the endolymphatic surface of the tissue, this barrier seems to be destroyed about two hours after death of the animal permitting free pass of the reagents through it. When the stria vascularis exposed to post mortem changes was incubated in a solution of the reagents, the red coloration diffusely began in the entire portions of the tissue (Fig. 1). Further similar findings may be obtained if the cochlea was frozen by solid carbondioxide prior to staining (Fig. 1).

In conclusion the existence of the barrier between the lymphatic space and stria vascularis interferes obtaining precise pattern of distribution of the enzyme in the stria vascularis. Therefore if one would intend to observe the stria vascularis histochemically, the freezing method (Koide *et al*, 1962) seems to be preferable.

Differences in Enzymic Activities Between Each Turn

The cochleas were removed from the temporal bone of the guinea pigs and frozen by solid carbondioxide. One side of the cochlea was clipped off by means of a freezing microtome and turned upside down. The opposite side of the cochlea also was clipped off and the frozen specimen about 1-2 mm thick was obtained. The specimens were anaerobically incubated in a solution of the reagents for succinic dehydrogenase and/or DPN diaphorase at 37°C for the time to attain an appropriate coloration.

The reagents for DPN diaphorase were as follows

1 M	sodium malate	3 ml
	DPN	10 mg
1 M	sodium glutamate	5 ml
0.03 M	sodium cyanide	[illegible] ml
0.2%	neotetrazolium chloride	3.5 ml
0.1 M	phosphate buffer (pH 7.4)	11 ml
	ad aq dest	30 ml

1. *The stria vascularis*

First the contents of succinic dehydrogenase and/or DPN diaphorase were compared between the stria vascularis of each turn. As deep coloration due to too prolonged time of incubation may interfere the precise comparison of color intensity, the time of incubation should be controlled under a light microscope to attain an appropriate coloration.

In every specimen the development of the color in the stria vascularis was very rapid in the lower turn as compared with that in the middle and higher turns (Figs. 3 and 4). For example, when the specimens were treated with the reagents for succinic dehydrogenase, the distinct pink color became visible in the stria vascularis of the basal turn within few minutes of incubation and the coloration occurred in the middle turns after 5-7 minutes of incubation. But the development of color was very slow in the higher turns, especially in the apical turn.



FIG. 2. The specimen was prepared by the routine method for succinic dehydrogenase. The lower and upper portions of the stria vascularis are stained darker.

The specimens were anaerobically incubated in a buffered solution of the reagents for one hour at 37°C. After a rinsing with water, they were treated with 10 % formalin and examined under a light microscope.

The red color due to the formation of formazan appeared in the spiral ligament, especially in its lower portion. The reagents passed into the stria vascularis from its bilateral cut ends, showing the distinct red color in these portions, while the middle portion of the tissue remained colorless (Fig. 1). *Therefore it may be concluded that the endolymphatic surface of the stria vascularis is impermeable to some components of the solution.*

The color might sometimes appear in the upper and lower portions of the stria vascularis after prolonged incubation of the specimens, when they were prepared by the routine method (Fig. 2). This finding suggests that the reagents may be diffusible from the spiral ligament into the stria vascularis. On the basis of the findings described above, there are two possible pathways *of the reagents from the lymphatic space into the stria vascularis.* One is the damaged surface of the stria vascularis, another the way via the spiral ligament. Under these circumstances *the diffusion of the reagents from the lymphatic space into the stria vascularis may be very variable, depending on the local status of the tissue, and would produce very irregular development of color in the tissue.*

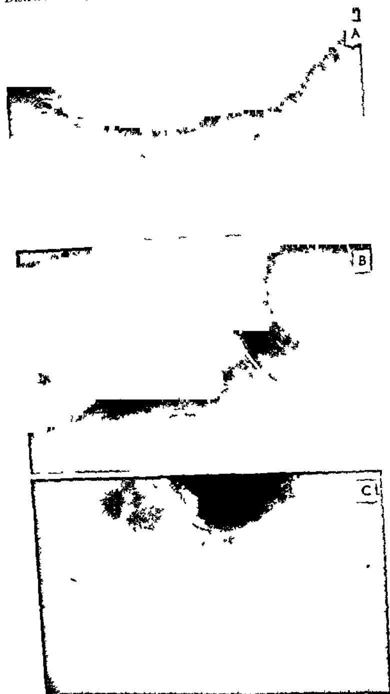


Fig. 4. The photographs were taken from one specimen prepared by the freezing method for DPN diaphorase. The stria vascularis looks darker in the lower turns than in the higher turns. The tissue remained colorless in the apical turn. *A*. The basal turn. *B*. the second turn. *C*. the third turn.

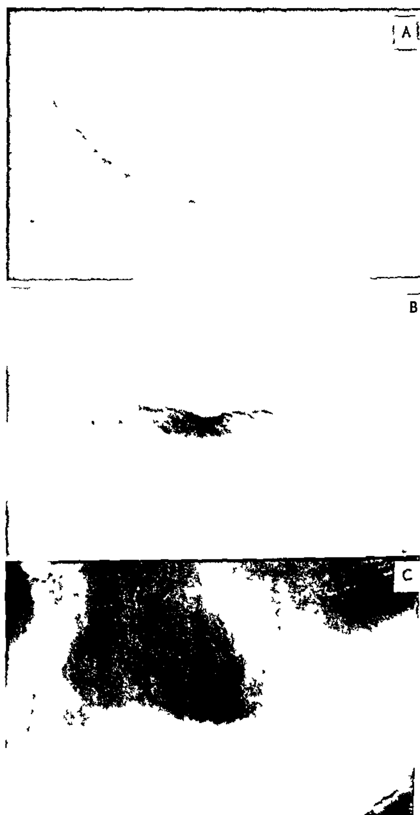


Fig. 3. The photographs were taken from one specimen prepared by the freezing method for succinic dehydrogenase. The stria vascularis looks darker in the lower turns than in the higher turns. The tissue remained colorless in the apical turn. *A* The third turn, *B* the second turn, *C* the basal turn.

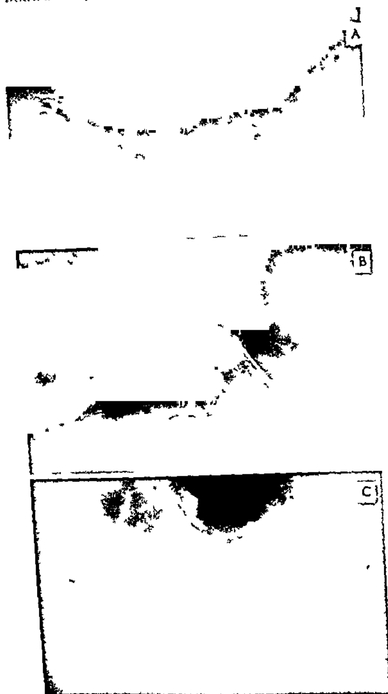


Fig. 4. The photographs were taken from one specimen prepared by the freezing method for DPN diaphorase. The stria vascularis looks darker in the lower turns than in the higher turns. The tissue remained colorless in the apical turn. A. The basal turn. B. the second turn. C. the third turn.

A



B



C

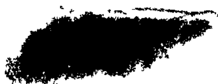


FIG. 5. The photographs were taken from one specimen prepared by the freezing method for succinic dehydrogenase. The spiral ligament looks darker in the lower turns than in the higher turns. The tissue remained colorless in the apical turn. *A*, the third turn; *B*, the second turn; *C*, the basal turn.

A



B



C



Fig. The photographs were taken from one specimen prepared by the freezing method for DPN diaphorase. The spiral ligament looks *darker in the lower turns* than in the higher turns. The tissue remained colorless in the apical turn. *A* The third turn. *B* the second turn. *C* the basal turn.

When the specimens were treated with the reagents for DPN diaphorase the development of color in the stria vascularis seems to be rather slow. But it was also more distinct in the lower turns than in the higher turns.

As the specimens were frozen prior to the staining the barrier which is the endolymphatic surface of the stria vascularis seems to be destroyed. There

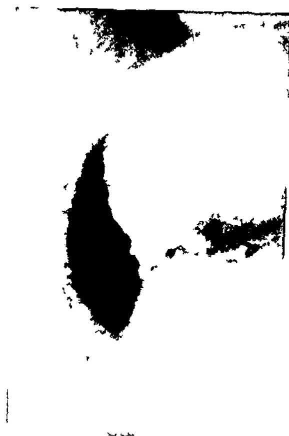


Fig. 7. The specimen was prepared by the freezing method, showing higher concentration of succinic dehydrogenase in the outer hair cells than in the inner hair cells.

fore it may be considered that the differences in the coloration in the stria vascularis probably depend on the differences in the content of the enzymes.

2. *The spiral ligament*

The development of color of the stria vascularis always precedes that of the spiral ligament, when the specimens were treated with the reagents for the enzymes. Therefore longer time of incubation is needed to obtain the stained specimens where there are any discernible differences in the coloration of the spiral ligament.

The development of color in the spiral ligament was the most distinct in the basal turn and slower in the higher turns (Figs. 5 and 6). These findings suggest that both the enzymes of the spiral ligament may be richer in the lower turns than in the higher turns. Further it must be noticed that the main site of both the enzymes is located in the lower portions of the tissue in every turn.

3. *The organ of Corti*

Although there are differences in enzymic activities of the stria vascularis and/or spiral ligament between each turn, the organs of Corti, especially the

hair cells seemed to have revealed the same levels of enzymic activities in the entire turns That is the development of color was detectable at the same time of incubation in the entire areas of the cochlea when the specimens were treated with the reagents for enzymes And any differences in the coloration could not be observed throughout the experiments

However it may be suggested that there is a difference in the content of succinic dehydrogenase between the outer and inner hair cells Fig 7 shows the specimens where the outer hair cells were stained darker than the inner hair cells On the other hand there was no indication of the existence of a difference in the distribution of DPN diaphorase between both hair cells

COMMENT

Comparison of oxygen consumption of the isolated stria vascularis was made by the method of Cartesian diver manometry by Kawamoto & Kakizaki (1962) They have drawn the conclusion that oxygen consumption was more active in the lower turns than in the higher turns In their experiments succinate was used as substrate and the results were expressed in μl of oxygen per unit length of the tissue for a period of incubation of 10 30 and 60 minutes at 37°C

Nakai (1963) has carried out similar experiments and has concluded that oxygen consumption of the isolated stria vascularis was the most active in the middle turns and not so active in both the lower and higher turns In his experiments oxygen consumption was also expressed in μl of oxygen per mm of the tissue length for a period of incubation of one hour at 37°C

It may be said that the stria vascularis appears to reduce its size in the higher turns Therefore a question arises Is their expression of the rate of oxygen consumption reasonable? During the past years we have carried out some experiments which might be related to the above question As a first approach to this question glucose utilization of the isolated stria vascularis and/or spiral ligament was measured In these experiments glucose utilization was expressed in μg of glucose per mg of the dried tissue for a period of one hour at 37°C The results obtained were variable

In a heterogeneous system the reaction velocity would be influenced by size of the materials subjected to the examination and also by alteration of cell walls which may be produced during isolation and incubation of the materials Probably these are the cause of obtaining variable results and seem to be unable to be exactly controlled in each experiment Here it seems to be reasonable to conclude that the freezing method described in the present paper may be more reliable for the observation of oxidizing enzymes of the cochlear tissues than the routine biochemical methods are

As described it became clear that concentration of the oxidizing enzymes is larger in both the stria vascularis and lower portions of the spiral ligament of the lower turns than in those of the higher turns Then it may be imagined that difference of concentration of the oxidizing enzymes between each turn

would be required in order to demonstrate any difference in the cochlear function between each turn.

The endolymphatic DC potentials may be noticed here. According to Misrahy *et al.* (1958) the DC potentials were as high as 110–120 mV in the basal turn, 90–100 mV in the second turn, 80 mV in the third turn, and 0 mV in the apical turn. However, Gisselsson (1960) has reported that there were no differences in the DC potential between each turn. According to Kawata *et al.* (1962) the DC potentials were 70–90 mV in the basal turn and 60–70 mV *in the apical turn. They have concluded that there is the existence* of nearly the same DC potentials throughout the entire cochlea.

Therefore it may be impossible to conclude whether the differences in the enzymic activities of the stria vascularis and/or spiral ligament between each turn relate in any way to the differences in the cochlear function between each turn.

ZUSAMMENFASSUNG

Die cochlearen Exemplare, durch die Gefriermethode bereitet, konnen mit Erfolg der genauen histochemischen Untersuchung uber die Verteilung von succinischer Dehydrogenase und/oder DPN-Diaphorase ausgesetzt werden. Die folgenden Ergebnisse wurden mit dieser Methode erzielt.

1. Konzentration beider Enzyme sowohl der Stria vascularis als auch der unteren Teile des spiralen Ligamentes ist grosser in den unteren Krummungen als in den hoheren Krummungen.

2. Es bestehen keine Unterschiede in den enzymatischen Aktivitaten des Cortischen Organs zwischen jeder Krummung.

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L'ACTIVITÉ BIDIRECTIONNELLE DES CANAUX SEMI-CIRCULAIRES HORIZONTAUX CHEZ LA GRENOUILLE

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On a comparé, pour diverses valeurs de la stimulation, les réactions post-rotatoires chez des grenouilles dont l'appareil vestibulaire était intact et chez des grenouilles privées d'un canal semi-circulaire horizontal depuis un an. Ces réactions ont une amplitude plus faible et un seuil plus élevé dans le second cas que dans le premier. On en conclut que, lorsque l'appareil vestibulaire est intact, les deux canaux horizontaux participent à la fois aux réactions dans les deux sens.

INTRODUCTION

La question du sens de stimulation des canaux semi-circulaires — unidirectionnalité ou bidirectionnalité — a été posée par Crum Brown (1874). Après la première étude expérimentale, celle d'Ewald (1892), de nombreux travaux ont été consacrés à ce problème, surtout dans le cas des canaux horizontaux (ou externes).

Chez l'Homme, un canal semi-circulaire horizontal est bidirectionnel tant en l'absence qu'en la présence du labyrinthe opposé, et la stimulation est en moyenne d'égale efficacité dans les deux sens (Buys 1925, Fitzgerald & Hallpike 1942, Van Egmond, Groen & Jongkees 1949, Niven & Graybiel 1953).

Chez les autres Vertébrés, Mammifères y compris, les résultats sont partiels et dispersés, parfois contradictoires pour une même espèce. Certains auteurs ont étudié les effets de la stimulation rotatoire d'un canal horizontal après suppression du labyrinthe ou du canal horizontal opposé (la vision étant exclue, bien entendu). Ces recherches ont porté sur les Poissons (Loewenstein 1932, 1937), la Grenouille (McNally & Tait 1925, Gribenski 1957), le Pigeon (Van Eyck 1954), et leurs résultats sont concordants: après suppression d'un canal horizontal, l'autre est d'abord unidirectionnel (il n'est stimulé que par des courants d'endolymphe ampullopètes), mais il devient bidirectionnel quelques jours ou quelques semaines plus tard (il est alors stimulable aussi par des courants ampullofuges).

D'autres auteurs ont étudié les effets de courants d'endolymphe ampullopètes et ampullofuges produits dans un canal semi-circulaire horizontal par une action calorique ou mécanique, le labyrinthe opposé étant intact. Parmi ces travaux figurent ceux de Lorente de Nó (1926) sur le Lapin et de

Gernandt (1952) sur le Chat qui concluent à la bidirectionnalité. A l'opposé les expériences de Steinhausen (1933) et de Vilstrup (1950) sur le Chat et le Chien, de Van Eyck (1951) sur le Pigeon conduisent à penser que seuls les courants ampullopètes donnent naissance à des réflexes, les courants ampullofuges ayant une efficacité nulle ou presque nulle.

A la lumière des travaux cités précédemment, il apparaît que le problème du sens de stimulation pour les canaux horizontaux se décompose en plusieurs questions:

1° Un canal horizontal peut-il donner naissance à des réactions dans les deux sens après suppression de l'autre canal horizontal, soit aussitôt après cette suppression, soit au terme d'une période de compensation?

2° Un canal horizontal a-t-il un fonctionnement bidirectionnel ou unidirectionnel chez un animal dont les deux labyrinthes sont intacts? En d'autres termes, les deux canaux participent-ils à la fois aux réactions dans les deux sens, ou bien chaque canal produit-il seulement les réactions dans l'un des sens?

3° Dans le cas où l'on admet la bidirectionnalité, l'effet de la stimulation est-il — ou peut-il être — équivalent dans les deux sens? En d'autres termes, un courant ampullopète et un courant ampullofuge mécaniquement équivalents ont-ils — ou peuvent-ils avoir — la même efficacité?

On sait par ailleurs que l'activité électrique du nerf ampullaire d'un canal semi-circulaire est bidirectionnelle: pour les canaux horizontaux, un courant d'endolymphe ampullopète accroît l'activité électrique du nerf, tandis qu'un courant ampullofuge produit une inhibition de cette activité (Loewenstein & Sand 1936, 1940, Gernandt 1949, Ledoux 1958). Admettre la bidirectionnalité des canaux horizontaux, c'est donc admettre que des réflexes peuvent être déterminés tant par l'inhibition que par l'accroissement de l'activité électrique du nerf. Si, au contraire, les canaux horizontaux sont unidirectionnels, cela signifie que seul l'accroissement de cette activité peut produire des réflexes.

EXPÉRIENCES ET RÉSULTATS

Des expériences antérieures nous ont permis de répondre, dans le cas de la Grenouille, à la première des questions posées ci-dessus: un canal horizontal en effet peut être stimulé par des courants d'endolymphe de l'un et l'autre sens lorsque le canal horizontal opposé est supprimé depuis quelques jours ou quelques semaines (Gribenski 1957). Le présent travail cherche à répondre à la seconde question: chez une Grenouille dont l'appareil vestibulaire est intact, les deux canaux horizontaux participent-ils à la fois aux réactions dans les deux sens.

I. *Méthodes*

Nous avons comparé les réactions postrotatoires de grenouilles ayant l'appareil vestibulaire intact et de grenouilles privées d'un canal semi-circulaire horizontal, pour diverses valeurs de la stimulation.

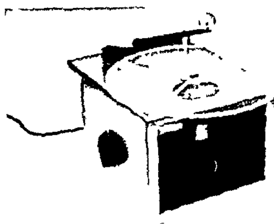


Fig 1 Appareil utilisé pour la stimulation rotatoire

L appareil utilisé (Fig 1) comprend un double plateau en plexiglass de 25 cm de diamètre entraîné par un moteur à courant continu qui lui communique un mouvement de rotation uniforme En modifiant la tension d alimentation du moteur on peut obtenir toutes les vitesses de rotation jusqu à 20 tours/minute (ou 120 degrés/seconde) Grâce à un inverseur de courant la rotation est possible dans les deux sens

Le plateau inférieur est solidaire de l arbre du moteur, le plateau supérieur (portant la grenouille) repose sur le premier qui l entraîne dans sa rotation mais il peut tourner librement autour de l axe (Fig 2) Un frein à patin de

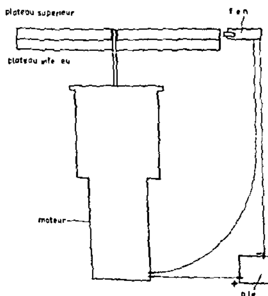


Fig 2 Dispositifs d entraînement et de freinage du plateau tournant

caoutchouc peut appuyer sur le bord du plateau supérieur, le déplacement du frein coupe en même temps le circuit d'alimentation du moteur, ce qui supprime le couple d'entraînement. La rotation peut ainsi être arrêtée brusquement de façon identique dans toute la gamme des vitesses utilisées.

Pour éviter toute interférence entre les réactions perrotatoires et les réactions postrotatoires, nous n'arrêtons la rotation que lorsque l'appareil vestibulaire est revenu au repos; des expériences préliminaires nous ont montré que, dans ce but, la rotation à vitesse uniforme doit durer une, deux ou trois minutes, selon la vitesse.

Dans ces conditions, la valeur de la stimulation due à l'arrêt brusque ne dépend que de la vitesse de rotation utilisée. Nous avons fait nos observations avec les 5 vitesses suivantes: 120 degrés/seconde, 35 degrés/s, 13 degrés/s, 6 degrés/s, 3 degrés/s.

L'espèce utilisée est la Grenouille verte (*Rana esculenta*). Tous les animaux de nos expériences étaient rendus aveugles par section des nerfs optiques afin d'éliminer l'influence de la vision sur les réactions postrotatoires.

II. *Résultats*

1) *Réactions postrotatoires des grenouilles dont l'appareil vestibulaire est intact*

La description qui suit se rapporte à une rotation de *sens horaire*.

Vitesse de rotation 120 degrés/s. La grenouille s'incurve fortement vers la droite, puis elle exécute un mouvement de manège (un ou plusieurs tours) dans le sens horaire; elle s'arrête ensuite en restant incurvée vers la droite. L'incurvation dure une ou plusieurs minutes, puis, par un mouvement brusque, l'animal reprend une attitude symétrique.

Vitesse de rotation 35 degrés/s. La grenouille s'incurve vers la droite et parfois se déplace un peu en tournant dans ce sens (une fraction de tour).

Vitesse de rotation 13 degrés/s. La grenouille s'incurve vers la droite sans jamais se déplacer.

Vitesse de rotation 6 degrés/s. La grenouille déplace légèrement la tête vers la droite.

Vitesse de rotation 3 degrés/s. En général, il n'y a pas de réactions.

Les réactions sont les mêmes pour des rotations de sens antihoraire; il suffit, dans la description qui précède, de remplacer le mot *horaire* par le mot *antihoraire* et d'intervertir les mots *droite* et *gauche*.

En résumé (Fig. 3):

1° Les deux sens de rotation sont équivalents et donnent naissance à des réactions égales mais de sens inverse.

2° L'amplitude des réactions diminue avec la vitesse de rotation; les réactions, encore perceptibles pour tous les animaux si la vitesse est de 6 degrés/s, ne le sont plus, en général, avec une vitesse de 3 degrés/s. Le seuil de stimulation correspond donc à une vitesse intermédiaire.

Ajoutons qu'une grenouille normale n'a pas plus de tendance à tourner d'un côté que de l'autre si on la soumet à un mouvement de rotation dirigé

Fig. 3

Fig. 4

Fig. 3. Réactions postrotatoires lorsque l'appareil vestibulaire est intact. Sens de la rotation: H horaire, AH antihoraire. Vitesses de rotation: ligne A 120°/s, B 35°/s, C 13°/s, D 6°/s, E 3°/s.

Fig. 4. Réactions postrotatoires un an après la suppression du canal horizontal gauche. G1, G2: deux grenouilles prises pour exemples. Sens de la rotation: H horaire, AH antihoraire. Vitesses de rotation: ligne A 120°/s, B 35°/s, C 13°/s, D 6°/s, E 3°/s.

alternativement dans un sens et dans l'autre, l'accélération et la durée étant les mêmes dans les deux sens, elle ne se déplace pas sur le plateau: elle se contente, chaque fois que le mouvement change de sens, de tourner la tête dans le sens opposé à celui de la rotation.

2) *Les réactions postrotatoires après élimination d'un canal semi-circulaire horizontal*

Chez la Grenouille, il est possible de supprimer un canal semi-circulaire, du point de vue fonctionnel, en coupant son nerf ampullaire (McNally & Tait 1925). Cette opération ne touche pas les autres récepteurs vestibulaires et ne modifie pas la posture de l'animal. Des précautions doivent être prises pour que le nerf ne régénère pas sa partie périphérique et il convient de contrôler, à la fin des expériences, l'élimination du canal semi-circulaire considéré (Gribenski 1957).

Lorsqu'on supprime ainsi un canal horizontal, il apparaît une dissymétrie tonique qui se manifeste par une vive tendance de l'animal à tourner vers le côté opéré, soit spontanément, soit à la suite de stimulations diverses; si l'on soumet la grenouille à un mouvement de rotation dirigé alternativement

dans un sens et dans l'autre, elle se met aussitôt à tourner vers le côté opéré et continue à se déplacer dans le même sens aussi longtemps que dure la même stimulation alternative. En outre, comme on va le voir, les réactions rotatoires sont profondément modifiées. La description qui suit est celle des réactions postrotatoires; elle se rapporte à une grenouille privée du canal horizontal gauche (pour une grenouille privée du canal horizontal droit, il suffirait d'intervertir les mots *droite* et *gauche*, *horaire* et *antihoraire*).

ROTATION DANS LE SENS HORAIRE.

Vitesse de rotation: 120 degrés/s. La grenouille reste immobile, il n'y a pas de réaction.

Vitesse de rotation: 35 degrés/s: pas de réaction.

Vitesse de rotation: 13 degrés/s: pas de réaction.

Vitesse de rotation: 6 degrés/s: pas de réaction.

Vitesse de rotation: 3 degrés/s: pas de réaction.

ROTATION DANS LE SENS ANTIHORAIRE.

Vitesse de rotation: 120 degrés/s. La grenouille s'incurve vers la gauche, puis exécute un mouvement de manège dans ce sens.

Vitesse de rotation: 35 degrés/s. La grenouille s'incurve vers la gauche et parfois exécute une fraction de tour dans ce sens.

Vitesse de rotation: 13 degrés/s. La grenouille s'incurve légèrement vers la gauche.

Vitesse de rotation: 6 degrés/s. La grenouille fait un petit mouvement de tête vers la gauche ou bien ne réagit pas.

Vitesse de rotation: 3 degrés/s: pas de réaction.

En résumé, les réactions dirigées vers le côté intact sont abolies, tandis que sont conservées les réactions dirigées vers le côté opéré. La suppression du canal horizontal gauche, par exemple, fait disparaître les réactions dirigées vers la droite; le canal horizontal droit, qui est alors seul présent, ne donne donc naissance à des réactions que s'il est stimulé par un courant d'endolymphe ampullopète et ces réactions sont dirigées vers la gauche. Ajoutons que ces réactions vers la gauche sont légèrement plus faibles que celles des grenouilles dont l'appareil vestibulaire est intact, mais cette différence est en partie masquée par la tendance que possèdent les grenouilles opérées à tourner vers la gauche (côté opéré).

3) *La compensation et les réactions postrotatoires après un an de compensation.*

Au cours des semaines qui suivent l'opération, la tendance à tourner vers le côté opéré s'atténue; en même temps, il apparaît des réactions rotatoires dirigées vers le côté intact, réactions dont l'amplitude, d'abord très faible, s'accroît avec le temps. Les réactions ainsi apparues à la faveur de la compensation sont dues à des courants d'endolymphe ampullofuges dans le canal conservé et montrent que de tels courants sont maintenant efficaces.

Un an après l'opération, la dissymétrie tonique est devenue très faible et les réactions ont lieu dans un sens ou dans l'autre, selon le sens de la rotation. Voici la description des réactions postrotatoires pour une grenouille privée du canal horizontal gauche.

ROTATION DANS LE SENS HORAIRE

Vitesse de rotation 120 degrés/s: La grenouille s'incurve vers la droite sans se déplacer.
Vitesse de rotation 30 degrés/s: La grenouille s'incurve légèrement vers la droite.
Vitesse de rotation 13 degrés/s: La grenouille déplace légèrement la tête vers la droite.
Vitesse de rotation 6 degrés/s: pas de réaction.
Vitesse de rotation 3 degrés/s: pas de réaction.

ROTATION DANS LE SENS ANTIHORAIRE

Vitesse de rotation 120 degrés/s: La grenouille s'incurve *fortement* vers la gauche, sans se déplacer.
Vitesse de rotation 30 degrés/s: La grenouille s'incurve *légèrement* vers la gauche.
Vitesse de rotation 13 degrés/s: La grenouille déplace la tête vers la gauche ou s'incurve légèrement de ce côté.
Vitesse de rotation 6 degrés/s: Selon le cas, la grenouille déplace légèrement la tête vers la gauche ou ne réagit pas.
Vitesse de rotation 3 degrés/s: pas de réaction.

Les réactions dans les deux sens sont dues à la stimulation du *même canal* horizontal. Par exemple, si le *canal supprimé* est le canal horizontal gauche, les réactions dirigées vers la *gauche sont dues* à des courants d'endolymphe ampullopètes dans le canal horizontal droit, les *réactions vers la droite* à des courants ampullofuges dans le même canal.

Toutefois, ces réactions sont plus *faibles que chez les* grenouilles possédant les deux canaux horizontaux. *Ainsi avec la plus forte* stimulation utilisée (vitesse = 120 degrés/s), la réaction est *seulement une* incurvation du corps sans mouvement de manège (Fig. 4). En outre, il y a souvent une élévation du seuil; en effet, la *stimulation* avec la vitesse de 6 degrés/s, efficace pour toutes les grenouilles à *appareil* vestibulaire *intact*, est souvent inefficace (donc inférieure au seuil) *chez* les grenouilles possédant un seul canal horizontal (Fig. 4, G1).

Il faut enfin noter *que* les réactions dirigées vers la droite et vers la gauche ne sont en général pas *symétriques* (Fig. 4). Si, comme dans les exemples précédents, le canal *supprimé est le* canal horizontal gauche, l'amplitude est un peu plus grande pour les *réactions* dirigées vers la gauche que pour les réactions vers la droite. Chez *certains* de ces animaux, en outre, le seuil

est plus bas pour les réactions vers la gauche que pour les réactions vers la droite (*Fig. 4, G2*).

CONCLUSION

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Wir haben mit Hinsicht auf verschiedene Reizungswerte die postrotatorischen Reaktionen bei Froschen, deren Vestibularapparatus unberuhrt war mit denen von Froschen verglichen, welche seit einem Jahr eines horizontalen Bogengang verlustig waren Diese Reaktionen haben im Vergleich zum ersten Fall eine schwachere Weite und eine hohere Schwelle im zweiten Fall Wir haben die Folgerung gezogen dass, wenn der Vestibularapparatus unversehrt ist die zwei horizontalen Kanale sich zu gleicher Zeit an den Reaktionen nach den zwei Richtungen beteiligen

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TONSILLOGENIC PROCESSES IN THE LIGHT OF PRESENT DAY KNOWLEDGE OF THE TONSILLAR NERVOUS APPARATUS MORPHOLOGY AND FUNCTION

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As apparent from recent neurohistological investigations, the lymphadenoid pharyngeal ring comprises an intricate nervous apparatus which contains different elements of afferent and efferent innervations During the foetal and postnatal periods the nervous apparatus of the lymphadenoid pharyngeal ring undergoes a certain reconstruction In chronical tonsillitis the nervous apparatus of tonsils exhibits a series of structural changes, mostly of reversible character The intricate structure of the nervous apparatus in the lymphadenoid pharyngeal ring its age properties and definite changes with pathological processes must be taken into account when considering clinical data

Polymorphism of tonsillar receptors yields evidence in favor of variety in their receptor functions and neuroreflex connections with different organs, including the heart whose close neuroreflex interconnections with the tonsils have been revealed in clinico experimental observations (tonsillo cardiac reflex) Reconstruction of nerve elements in the lymphadenoid pharyngeal ring during man s life as well as their involvement in pathological processes have a certain influence on the age properties of the tonsillar receptor funct on enabling the tonsils to exert a neurotrophical effect pervert pathological discharges The last mentioned facts not only impair the barrier function of pathologically changed tonsils but contribute to the development of diseases which tonsillar origin is attributed to

The tonsillar problem includes a range of various questions closely associated with each other To find an adequate prophylaxis or treatment for different affections of tonsils and allied diseases one should have a distinct concept of the part the tonsils play in pathology as well as of the mechanism of tonsillogenic processes And the part of tonsils in pathology cannot be evaluated without a profound knowledge of their structural and functional properties

For all that structure and function both normal and pathological of the lymphadenoid pharyngeal ring still remain unknown in more than one respect Especially little consideration has been given to morphology and function of the tonsillar nervous apparatus

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Reçu le 10 mars 1964

structure of vascular and vascular tissue receptors proves to be very intricate The intricacy of vascular innervation of tonsils apparently depends on their rather variable trophics the tonsils are especially subject to evolution and involution they respond dramatically to alimentary toxical and other factors

In the period of pubescence the palatine tonsils contain receptor endings with a multitude of large reticular plates which at other stages of development occur only in the pharyngeal tonsil This fact allows of suggesting the above type of nerve endings to play the part of a temporary device to enhance the reception in the palatine tonsils during the period of their greatest activity

Although the argyrophil properties of the nerve elements contained in tonsils usually become markedly reduced at the period of pubescence one can still reveal those elements in different tissues including the epithelium and follicles

The tonsillar follicle innervation has its origin in the interfollicular nerve plexuses which comprise both non myelinated and myelinated nerve fibres Naked axis cylinders are found in follicles together with *receptor endings in* form of reticulars The presence of receptor endings in follicles testifies to the possibility of afferent discharges on the part of the most active *tonsillar component*

Great variety in tonsillar nerve elements must stipulate the variety of their functions It seems beyond doubt that basing merely on *morphological properties* once can hardly assess in a proper way the functional *value of some* or other nerve elements Especially difficult it is in respect to receptors which do not appear to be stable structures (Lavrov 1941 Davydovsky *1954) But* yet some considerations can be put forward

The nerve plexuses lying in tonsils as was stated above are composed of non myelinated and myelinated fibres The former prevail in number the latter are largely *fibers of small* and middle calibre The functional difference of all those conductors will be evident if we consider their characters to be entirely dependent *on presence* or absence of medullary sheath on its thickness and on the calibre of nerve fibres It is well known e g that the vegetative fibres are characterized either by having a thin medullary sheath or not having any medullary sheath at all *(Orbeli 1935* Pines 1940) the main bulk of non myelinated and small *myelinated* fibres *belonging to the* sympathetic conductors (Shargorodsky *1946)* The myelinated fibres of middle and small calibre are *thought to be of* sensory type (Kiss & Mihalik 1929 Favorsky 1930 and others) *Some data* are available on the correlation between the calibre of myelinated *fibres and the* type of sensation (Ranson 1931 Hamabe 1932)

The tonsillar receptors which prove to be *terminals* of fibres differing in calibre exhibit marked variations There are both non encapsulated and encapsulated receptors *among them* The receptor endings lying in the tonsillar epithelium are likely to subserve touch and pain The clew shaped receptors lying in subepithelium and conjunctive tissual stroma of tonsils can

The literature on that subject offered but a few researches with brief and sometimes contradictory results. Within recent years there has appeared a series of new publications concerned with the problem of the tonsillar nervous apparatus (Sasosov, Isakov, Soldatov 1952, Sasosov 1952, 1956, 1960, Mletchin 1952, 1953, 1957, Piscun 1952, 1953, 1955 and others).

As the lymphadenoid pharyngeal ring is greatly subject to age changes which being closely connected with changes in the whole body reactivity may exert a certain influence on the clinical manifestations of different tonsillar affections, we have studied the nervous apparatus of the palatine, lingual, pharyngeal and tube tonsils in the aspect of its development and age properties; besides, we have carried on some investigations of tonsillar nerve elements in a series of diseases typical of tonsillar pathology, including chronical tonsillitis (Soldatov 1953, 1955, 1959, 1962).

The results of our research make us, first of all, flatly reject the conception of tonsils being poorly innervated formations with very limited, if any, reception (Abderhalden 1926, Schiever & Strughold 1926, Parkinson 1951 and others). Both palatine tonsils and other components of the lymphadenoid pharyngeal ring—the lingual, pharyngeal and tube tonsils—have a very intricate nervous apparatus comprising different elements of afferent and efferent innervation. The nerve elements contained in tonsils are represented by a conductor apparatus (nerve plexuses formed by afferent and efferent fibres), a nerve cellular apparatus (single nerve cells and nerve knots with intercellular plexuses and pericellular formations) and nerve endings (including various receptors). It is noteworthy that the structure of the tonsillar receptor apparatus in man is far more intricate than that of tonsillar receptors in experimental animals (cats); it exhibits a far greater variety of forms. The fact that the tonsils have nerve cells (usually met with in the palatine and lingual and occasionally in pharyngeal and tube tonsils) and pericellular apparatuses is a considerable support for the view that the tonsils possess both preganglionic and post-ganglionic nerve fibres. The nerve plexuses located in tonsils are composed of different kinds of conductors: along with non-myelinated nerve fibres prevailing in quantity there are also myelinated fibres of varied calibre (small and middle sized predominate).

There is a close interdependence between the development of the nervous apparatus and the formation of tonsils. In foetal and postnatal life the nervous apparatus of the lymphadenoid pharyngeal ring undergoes a certain reconstruction to show considerable age changes.

The most complete development is reached by nervous apparatus of the lymphadenoid pharyngeal ring in the period of pubescence when the tonsils are characterized by ultimate formation of their components. In this period it is the powerful development of afferent nerve supply elements that our attention is particularly attracted to. The receptor endings exhibit a marked polymorphism. Along with receptors richly or poorly ramified the tonsils always contain some receptor endings in form of encapsulated or non-encapsulated clews, a lot of them being provided with specific cells. The

tonsils It is not the structure of the nervous apparatus but rather its functional conditions varying in different components of the lymphadenoid pharyngeal ring that evidently play an important part in pathology And those conditions dependent primarily on the structural peculiarities of the lymphadenoid pharyngeal ring components prove to be quite particular as far as the nervous apparatus of the palatine tonsils is concerned In fact the palatine tonsils—the largest components in the lymphadenoid pharyngeal ring lodged at the junction of the respiratory and digestive tracts unlike other tonsils are provided with deep lacunes Being a good nutrient medium for all kinds of bacteria the lacunar contents does contribute to a permanent irritation of the afferent link in the tonsillar nervous apparatus

Polymorphism of tonsillar receptors elucidates the variety of their receptive function and neuro reflex connections with different organs including the heart the close neuro reflex interrelation of the latter with the tonsils have been brought to light in clinico experimental observations (certain electro cardiographic shifts provoked by tactile painful or thermal irritation of palatine tonsils—tonsillocardial reflex) carried on together with Sasosov & Isakov (1959) and confirmed in the clinics directed by Nesterov (Volkova 1956) and Lebedev (Bogomolova 1960)

It has been proved both by recent experimental investigations and clinical observations that the stimulus localized within the tonsils greatly affects the development of cardiac changes Of particular interest are the experiments on puppies carried out by Lebedev and co authors (Lebedev & Petrov 1956 Lebedev Petrov & Sopelkina 1959 Lebedev Petrov & Sokolkina 1960) Some puppies were given turpentine injections into the thickness of the tonsils others—into the thigh muscle The electrocardiographic shifts appeared only in the first group of puppies One of the experimental animals has been under observation for two years Along with E C G changes there were revealed certain changes on microscopical examination of the heart viz thickening of small arterial and arteriolic walls perivascular oedema individual vessels intima infiltrated by lymphoids

Some interestin[illegible]
reflex are referre[illegible]
(1959 1961) Ser[illegible] [illegible] observed cardio vascular changes in experimental quinsy noticed similar changes upon stimulating the vagosympathicus brought out into a skin flap she points out that in experimental quinsy a change occurs in vago sympathic conductivity (in part of cases even a full cessation) which manifests itself either by rise or by drop of stimulus threshold Bogomolova reports on the tonsillo cardiac reflex being absent in puppies during atropin intoxication and changing in result of an unilateral cervical vago sympathetic blocade The change of tonsillo cardial reflex in puppies upon unilateral decortication allowed F A Bogomolova to infer that reflex arc is not completed in subcortex it proceeds into the brain cortex the tonsils having mostly a direct and not a cross innervation

The tonsillo cardial reflex which appears to be an unconditioned reflex

bear relation to mechano- or baroreception. However, too great a variety in forms, dimensions, compactness of clews, as well as in calibre and even quantity of fibres which those nerve endings are composed of, allows us to believe their function not to be confined only to mechanoreception alone. Their possible participation in thermo- and osmoreception should not be excluded either. This, however, requires special evidence: today neither physiology nor morphology have data available to put thermoreception or osmoreception into connection with any definite nerve endings (Tchernigovsky, 1960).

Receptor endings of intricate structure with specific cells which are most frequent in the subepithelial layer of tonsils may be included in the category of chemoreceptors—announcers of metabolic changes.[1] As is generally known, the specific (or adjunct) cells are believed to be of great importance in transforming the stimulating energy into nerve exciting process (Lavrentiev, 1948). As for the past few years, the character and localization of structures subserving transformation of stimulus into nervous process have been successfully studied by histochemical methods of investigation (Portugalov, 1955).

Vascular and vascular tissue receptors which control the physico-chemical processes of circulation appear to be frequent in tonsils. For the time being it is difficult to assess the function which is performed by receptor endings with a great many large reticular plates always occurring in the lymphadenoid tissue of the pharyngeal tonsil and belonging to myelinated fibres of a rather significant calibre. Perhaps they are mechanoreceptive in function.

Great variety in tonsillar nerve elements gives evidence of the important part played by the nervous mechanisms in performing the principal function —the protective one— of the lymphadenoid pharyngeal ring.

Reflex reactions called forth by stimulating with lacunar contents the afferent link of the tonsillar nervous apparatus may be of vital importance in the immunogenetic process.

Do the principal components of the lymphadenoid pharyngeal ring exhibit any difference in the structure of their nervous apparatus? If so, could we not take advantage of these structural properties to interpret the clinical observations saying that the palatine tonsils are involved in pathological processes far more frequently than other tonsils? Our investigations have proved the nervous apparatus of different tonsils to have some characteristic features in their structure. So, e.g., it is especially typical of the pharyngeal tonsil to have receptor endings with a great many large reticular plates. The palatine and lingual tonsils always contain nerve cells and collections of nerve cells while in the pharyngeal and tube tonsils they occur very rarely. For all that, we have no sufficient reason to assert that the nervous apparatus of the palatine tonsils substantially differs in structure from those of other

[1] The presence of chemoreceptors in tonsils (Soldatov, 1953) has been confirmed by Ilkunova's investigations (1956).

place too Among nerve endings with reactive changes one reveals receptors showing peculiar signs of irritation which resemble end neuromasts Part of nerve cells contained in palatine tonsils exhibit in chronical tonsillitis indistinct outlines redistribution of chromatophyll substance nuclear hyperchromatosis and body shrinkage

Patients with chronical tonsillitis often complain of pressure sense burning or sore throat Occasionally there occur ear tooth jaws and larynx pains (Preobragensky 1938 1954) Cvtovitch (1916 1925) has often observed fits of emetic cough in chronical tonsillitis Dudarev (1946) described epi leptic attacks that disappeared upon removing pathologically changed palatine tonsils In addition some observations are available on the effect of chronical tonsillitis resulting in bronchial asthma (Cvtovitch 1916) and an gina pectoralis (Volovik 1939) attacks

Not only the data we have referred to but many other clinical observations testify to a rather frequent occurrence of varied neuroreflex troubles in chronical tonsillitis Those troubles are no doubt associated with certain pathological changes in the nervous apparatus of chronically inflamed palatine tonsils

Pathological changes of nerve elements taking place within a wide range—from early stages to the end of degenerative process—must also provoke a series of troubles in normal function of the nervous apparatus of palatine tonsils Those troubles in their turn will no doubt disturb in a certain way the function of some organs and systems particularly that of the heart whose close neuroreflex interrelations with tonsils have been revealed in our clinico experimental observations (*Sasosov Isakov Soldatov 1952*)

Pathological changes of receptor endings contained in tonsils of patients with chronical tonsillitis enable us also to elucidate some of the later clinico experimental findings So e g Goreva (1953) and Karabaeva (1956) who studied vascular reactions to stimulation of the palatine tonsils observed *that* those reactions were perversed in chronical tonsillitis This fact conforms with the result of our investigations in chronical tonsillitis one encounters in tonsils along with receptor endings of normal structure also receptors which have undergone reactive *changes*

The above considerations seem to be consistent with the well known state *ment of* Lavrentjev (1948) concerning the significance of reactive changes *in receptor endings* *One can hardly* doubt that reception from so changed apparatuses will be a different one said the eminent Soviet neuromorpho logist Regarding the receptors as announcers of tissual and cellular changes both in metabolism and structure Lavrentjev (1948) pointed out that disturbed receptor system can become by itself a cause of trouble in the coor dinating system *and consequently* provoke metabolic perversion structural changes reduction of cellular differentiation—all that being a morbid pro cess

Thus the pathological process in chronical tonsillitis *involves without fail* the tonsillar nervous apparatus and first of all its afferent link which is

can be made use of to produce conditioned reflexes. So, e.g. if we combine sound signals with mechanical stimulation of the palatine tonsils we shall be able to obtain (after 4–8 combinations) some E.K.G. changes only by means of sound stimuli alone. That conditioned auro-cardial reflex may serve as one of the objective methods to test hearing (Meunargia 1958).

Thus, the clinico-experimental and morphological investigations enable us to bring forward the problem of tonsillar receptor function and neuro-reflex relations with some of the internal organs, particularly the heart (tonsillo-cardial reflex).[1] The receptor function in other components of the lymphatic organ system—spleen, lymphatic nodules and marrow—was demonstrated by Tchernigovsky & Yaroshevsky's (1953) physiological experiments while the receptor endings in lymphatic nodules in man were described by Godinov in 1950.

Among the most important sections of the tonsillar problem the central place belongs to chronical tonsillitis and allied diseases. Many a conception exists reflecting different views on the part played by the tonsils in pathological processes. It is evident from all observations that whatever position the investigator takes in regard to the part of the tonsils in pathology he has to consider the importance of their nervous apparatus and nervous connections with other organs and systems.

The topographical and structural properties of the lymphadenoid pharyngeal ring, in the first place those of the palatine tonsils, favor the affection of the latter by all sorts of damages and the development of a steady inflammatory reaction in their tissue. But "any local process always arising on the base of some general factors at a certain stage of its development becomes itself a starting point of substantially new relations between local and general" (Davydovsky 1954). "A local inflammatory process appears to be a stimulating centre which through a receptor system involves into reaction the body nervous system" (Vail 1953).

As apparent from our investigations, it is the afferent ring in the nervous apparatus of palatine tonsils that undergoes most suffering in chronical tonsillitis. Pathological changes of nerve elements being rather varied prove to be largely reversible. They always occur in patients liable to anginas as well as in patients with recidivating paratonsillar abscesses. Nerve element injuries varying in severity are encountered both in tonsils removed between two anginal attacks and in those removed during paratonsillitis or a paratonsillar abscess. Along with pathologically changed nerve elements the palatine tonsils of patients with chronical tonsillitis contain nerve fibres, nerve endings and nerve cells of normal structure.

Many a nerve fibre injury is characterized by signs typical of a periaxonal segmental process, however, a disintegration of axial cylinders is taking

[1] Sasosov presented at the First All-Russian Conference of Otorhinolaryngology 1956 some clinico-experimental data on neuro-reflex relations between the palatine tonsils and kidneys in the human (tonsillo-renal reflex).

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responsible for tonsillar receptor function and neuroreflex connections. Pathological changes of receptor *endings lead to perversed reception and* pathological discharges and that, in its turn, may contribute to functional disturbance in several organs as well as to some changes in reactivity of the organism as a whole, especially its sensitivity to different agents (infectional, toxical etc.). By their effect on the lymphadenoid tissual trophics the pat*hological changes in the tonsillar nervous* apparatus can extend functional and structural disturbances caused by inflammation. Thereby the barrier function of tonsils will be disturbed which makes for the development of decompensation. A vicious circle of pathological process is being established in this way.

While many a change in the tonsillar nervous apparatus can exert a harmful effect on the lymphadenoid tissual trophics and the course of its inflammatory and destructive *processes, some of the changes in nerve ele*ments (e.g. varicosities of nerve fibres, ball shaped bulges of receptor terminals) may be regarded, in the light of present-day knowledge, as phenomena of compensatory adaptive and regenerative character.[1] These processes can turn out to be a significant link in the chain of compensatory *adaptive and regenerative changes of lymphadenoid tissue and contribute* to an auspicious outcome of its inflammatory destructive changes in chronical tonsillitis.

As far as the mechanisms of tonsillogenic processes are concerned, great importance is attached in modern otorhinolaryngology to allergization, both *general and local. Lately, in the clinic directed by V. F. Undritz, there have* been obtained some results showing that severity of general allergization in different clinical forms of chronical tonsillitis corresponds to that of local allergic reaction in tonsillar tissues (Pigulevsky, 1957, 1961).

This point of view, however, can by no means reduce the significance of *the tonsillar nervous apparatus and* receptor function *in tonsillar pathology* if we take into account that the course of the allergic process depends, to a considerable extent, on the acting innervation of the tissues. So, on the basis of numerous experiments, Vyropaev (1940) came to the conclusion that "the peripheric nervous system plays an enormous and decisive role in the tissual allergic processes, *the reactive properties of the tissue being depen*dent on the condition of the nervous system, therefore the character of aller-

[1] According to Milenkov's (1958) results, the morphological substrate of the compensatory adaptive reactions of the *nervous system displays structural formations of two kinds*: permanent and transient (or newly originated). The former comprise a number of structures including poly-axon receptors, which are present in the tonsils too. The transient (extremely labile) formations include: lateral thorn shaped *appendices of nerve-cell dendrites*, *growth flasks*, Perroncito spirals, redundant growth of pericellular formations, Kugel phenomenon and varicosities, enlarged or newly appeared dendrite lamellas, gigantic binuclear and polynuclear neurons, multiplication of nerve cells, *proliferation of neuroglia*. A number of similar formations may also occur in chronical tonsillitis.

gic processes developing in that tissue can vary with the changes arising in the tissue due to different disturbances from the part of its nervous apparatus

There is enough evidence to consider acute tonsillitis a reaction of chronical inflammation focus (chronical tonsillitis) to all kinds of irritation this reaction resulting from a quite particular allergia which arises in a non tonsillar way (Karpov 1945) According to this point of view the palatine tonsils participate as a focus of permanent irritation by lacunar contents in a series of pathological processes when the reactive ability of the organism as a whole undergoes some changes The above statement is demonstrated in particular by different degrees of tonsillar affections observed in hemopoetic system diseases of varying severity The significance of tonsillar nervous apparatus in the genesis of tonsillar affections is confirmed from the position of this conception too Great importance is attached thereby to the tonsillar efferent innervation which conveys nervous impulses from the central nervous system to the tonsils as the seat of permanent irritation Moreover the part of tonsillar efferent innervation becomes evident if anginas and chronical tonsillitis are considered to be a possible consequence of other affections or pathological conditions of the whole organism or some of its systems (Preobragensky 1959)

The data concerning structural properties of the nervous apparatus in the lymphadenoid pharyngeal ring the clinico experimental observations on neuroreflex interrelations between the tonsils and the heart (tonsillo cardiac reflex) as well as the considerations upon the significance of the neuro reflex component in the mechanism of tonsillogenic processes may elucidate certain points in the tonsillar problem and extend our concepts of the part played by tonsils in pathology

The above facts and statements have shown that with pathological processes the tonsillar nervous apparatus undergoes some changes varying in grade and importance Its changes surely affect the inflammatory and distrophic (destructive) tonsillar lesions and influence the clinical course of the disease It is to be believed that the positive effect of the conservative methods of treatment for chronical tonsillitis is to a certain extent connected with the morphological and functional restoration of the tonsillar nervous apparatus since the changes of the latter are reversible in many aspects and the treatment is able to stimulate the compensatory adaptive processes in the tonsillar nerve elements

Watching the dynamics of pathological process in tonsils one should take into consideration the changes in their nervous apparatus the more so as morphological and functional disturbances of tonsillar innervation can affect the nervous system condition and the functions of other organs and systems of the organism

All that determines the significance of the tonsillar nervous apparatus and its pathological changes in the clinical manifestations of tonsillitis and allied diseases

RÉSUMÉ

L'examen neurohistologique des amygdales pratiqué dans ces dernières années, nous a révélé qu'il existe dans l'anneau lymphadénoide du pharynx un complex appareil nerveux contenant diverses éléments d'innervation afférente et efférente. Pendant la vie fœtale et postnatale cet appareil est sujet à une certaine reconstruction. Au cours de la tonsillite chronique, nous le voyons signaler les modifications destructives dont la plupart sont reversibles. Considérant les données cliniques nous devons apprecier la structure compliquée de l'appareil susdit, aussi ses modifications d'âge et celles qu'il subit durant les proces pathologiques.

Le polymorphisme des récepteurs tonsillaires prouve que leur fonction réceptrice est diverse, et qu'ils sont en contact nerveux et réflexe avec plusieurs organes, le cœur y compris — les inter-réactions cardio-tonsillaires étant décelées par des observations expérimentales et cliniques (réflexe tonsillo cardiaque). La reconstruction des éléments nerveux de l'anneau lymphadénoide du pharynx pendant la vie de l'homme et la participation de ces éléments dans les procès pathologiques ont leur repercussion sur les particularités d'âge de la fonction réceptrice des amygdales. Ces éléments nerveux rendent possible l'exertion de l'influence neurotrophique et font apparaître des impulsions perverses pathologiques. Ces derniers faits peuvent non seulement endommager la fonction de barrière des amygdales transformées d'une manière pathologique mais ils peuvent aussi favoriser les affections auxquelles on attribue une génèse tonsillaire.

ZUSAMMENFASSUNG

Die in den letzten Jahren durchgeführten neurohistologischen Untersuchungen der Tonsillen bezeugen, daß der lymphatische Rachenring einen komplizierten Nervenapparat besitzt, der verschiedene Elemente der afferenten und efferenten Innervation enthält. Während der Foetal- und Postnatalperiode wird der Nervenapparat einem bestimmten Umbau unterworfen. Bei chronischer Tonsillitis zeigt er eine Reihe Strukturveränderungen meistens reversibelen Charakters. Die komplizierte Struktur des lymphatischen Rachenringnervenapparates, seine Wachstums eigenheiten und gewisse Veränderungen während der pathologischen Prozesse, müssen klinisch berücksichtigt werden.

Die Tonsillarrezeptorpolymorphie beweist die Vielfältigkeit der Rezeptorfunktion und der Neuroreflexverbindungen der Tonsillen mit anderen Organen u. a. mit dem Herzen, dessen engere Neuroreflexwechselbeziehungen mit den Tonsillen durch experimental klinische Beobachtung bewiesen sind (Tonsillocardiacreflex). Der Umbau der Nervenelemente des lymphatischen Rachenringes im Laufe des Lebens, ihre Einfügung in pathologische Prozesse bewirken die Wachstumseigenheiten der Tonsillarrezeptorfunktion, bestimmen die Möglichkeit einer neurotrophischen Beeinflussung, verkehrter pathologischer Impulse. Die letzteren Fakten können nicht nur die Barrierenrolle der pathologisch veränderten Tonsillen beeinträchtigen, sondern auch eine bestimmte Wirkung auf die Entwickelung der Krankheiten, denen man eine Tonsillargenesis zuschreibt, ausüben.

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VISUAL CONTROL OF HABITUATION TO COMPLEX VESTIBULAR STIMULATION IN MAN

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Twenty men completed an experiment in the Pensacola Slow Rotation Room while it rotated for several hours at a rate of 45 deg/sec Subjects were immobile (relative to the room) except for habituation series which consisted of head movements restricted to one plane and to a particular quadrant of that plane Visual problems were presented with each head movement to one group of subjects another group made all head movements of the habituation series in darkness Tests conducted in darkness before and after the habituation series revealed pronounced reductions in nystagmus and subjective effects in the practiced quadrant only in the visual task group The other group showed no reduction of nystagmus in either the *practiced or unpracticed* quadrant This experiment considered together with another experiment just completed indicates that vision can be an important factor in habituation of human subjects to vestibular stimulation

INTRODUCTION

Reduction of nystagmus due to repetitive presentation of unnatural vestibular stimuli has been the subject of a number of recent experiments (Collins 1962 Crampton 1962 Fluur & Mendel 1963 Henriksson *et al* 1961 Lidvall 1962 Proctor & Fernandez 1963) During any one reaction vestibular nystagmus may be facilitated or suppressed by visual stimulation depending upon the presence or absence of relative motion between the subject and his visual surroundings (*Mowrer 1937*) The specific question under investigation is whether or not visual suppression of vestibular nystagmus during each of a series of vestibular stimuli (habituation series) will influence nystagmus habituation[1] as indicated by vestibular tests applied in darkness before and after the habituation series[2]

The operation of subtle factors is suggested by older studies which have indicated 1) that nystagmus habituation is prevented by vision in pigeons with heads free (Mowrer 1934 p 29) 2) that nystagmus habituation is

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... in detecting series decrements (cf Mowrer 1934 p 43 compare Paragraphs 8 and 9)

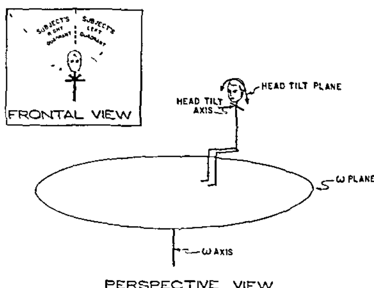


Fig 1 Illustration of planes and angular displacements used to elicit Coriolis vestibular reactions

specific to the response direction inhibited by vision in pigeons with heads fixed (Mowrer, 1934, p 35); and 3) that nystagmus habituation in pigeons is facilitated by vision (Abels, 1906) Many studies have shown that nystagmus habituation may occur in the absence of visual stimuli (Collins, 1962, Crampton, 1962, Mowrer, 1934, Proctor & Fernandez, 1963), but the extent to which this is attributable to reduced arousal is problematical (Collins, 1962, Guedry, *et al*, 1961) Wendt (1936, 1951) has suggested that nystagmus reduction with repetitive stimulation in the dark is attributable to increasing dominance of reverie states, but when visual reinforcement of still fixation is provided during the habituation series, nystagmus decline may be attributable to competition between visual and vestibular systems with vision gaining dominance Several studies (Brown & Guedry, 1951, Graybiel, 1963, Guedry, 1952) of subjective effects offer general support to Wendt's position but recent studies have indicated that vision does not facilitate nystagmus habituation (Crampton, 1962, Proctor & Fernandez, 1963) in any respect

Typically, experiments relevant to this issue have involved a routine introduction of light during or after passive angular acceleration of men (Brown & Guedry, 1951 Guedry 1952, 1953) or of restrained animals (Crampton, 1962, Mowrer, 1934 Proctor & Fernandez 1963) The present experiment differs from most of the previous studies in that it involves a) voluntary initiation of complex vestibular stimulation and b) voluntary (active) visual suppression of nystagmus in man

The complex sensory stimulation in the present experiment is noteworthy When the body rotates with constant velocity ω if the head is tilted to rotate about an axis (head tilt axis) orthogonal to ω axis (see Fig 1), each endolymph ring undergoes a change in angular momentum[1] Those en

[1] The author wishes to acknowledge helpful discussions with Dr Herman J Schaefer on the mechanics of rotation

dolymph rings in planes nearly orthogonal to both the ω plane and the head-tilt plane undergo a greater change in angular momentum per unit time than those rings which momentarily are nearly coplanar with the ω plane The *stimulus may* be conceptualized as an inertial torque about a third axis, orthogonal to ω axis and to the head tilt axis[1] Hence, during ω, when the head, initially upright, is tilted laterally in the frontal plane, an inertial torque would commence immediately to stimulate the vertical canals, but as the skull s sagittal plane departs this position, stimulation of the ' vertical canals would diminish while that of the ' horizontal canals' would increase Termination of the head tilt terminates this inertial torque but does not reverse its direction Thus the cupula is left in a deflected position to return to rest eventually by its inherent elasticity

During this time the otolith system would be principally influenced by change in orientation relative to gravity Hence the pattern of influx from the canals would be antisynergic to the intellectual, otolith, and proprioceptor information derived from the voluntary head movement, and the canalicular pattern itself could be bizarre with some movements

Because the unusual aspects of the stimulus to the canals during concomitant ω axis and head axis rotation about orthogonal axes can also be conceptualized as deriving from different magnitude Coriolis accelerations around the endolymph rings, the vestibular reaction in this situation has been named the Coriolis phenomenon (Meda 1952, Schubert, 1932) and the stimulus situation has been called the Coriolis vestibular stimulus (Bornschein, 1962, Guedry & Montague, 1961)

Graybiel *et al*, (1960) have introduced a fruitful line of experimentation wherein subjects are required to move the head or the whole body while enclosed in a slowly rotating room (SRR) Considerable difficulty in maneuvering as well as various neurovegetative symptoms are present initially, but after prolonged exposure, nystagmus illusory phenomena, and the neurovegetative symptoms decline markedly Results were obtained which suggested that vision enhanced the decline of the undesirable subjective effects (Graybiel, 1963)

In a recent experiment (Guedry, *et al*, 1964) in the SRR, *men rotated* for several hours and made a series of restricted head *movements in the* frontal plane (cf Fig 1) and in only one quadrant of this plane with the room illuminated Before and after the habituation series, head movements

in the unpracticed quadrant nystagmus response declines were slight During the habituation series, vision was permitted, but visual performance was not required

[1] Angular accelerations about the head tilt axis would be effective during the movement but at termination of head tilts of 90 degrees or less their net effect would be negligible due to the temporal proximity and opposite signs of the acceleration and deceleration

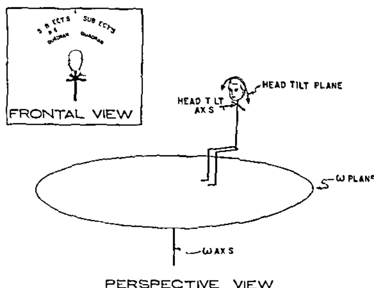


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... as not required ... as permitted, but visual performance

[1] Angular accele... at termination ... temporal proxi... ... and decelera'ion

The nature of the experiment, restricted repetitive head movement without apparent purpose, was conducive to drowsiness, and a few subjects occasionally closed their eyes, apparently inadvertently, during the habituation series, contrary to instructions. Some of these subjects failed to show a decline in nystagmus or subjective effects, and it was suspected that lowered attentiveness to the visual surroundings contributed to the deviant results

The present experiment differs from previous work (Guedry, *et al*, 1964) in one important respect During habituation as the head was moved, tests of mechanical comprehension and spatial relations were presented to one group of subjects by a slide projector, multiple-choice answers were required Thus with each head movement, executed in response to the click of the projector, a visual stimulus was presented which required voluntary control of eye movements when vestibular nystagmus would otherwise be expected to occur. Another group of subjects received the same habituation series in regard to vestibular stimuli but made all head movements in darkness The purpose of the experiment was to test the hypothesis that a visual task which enforces voluntary control of eye movements during vestibular stimulation will influence habituation evidenced by nystagmus and subjective effects.

METHODS

Experiments were carried out in the Pensacola Slow Rotation Room (SRR), a multi-sided room 15 feet in diameter and 7 feet high This room, described in detail elsewhere (Clark & Graybiel, 1961), is capable of prolonged constant angular velocity with little, if any, perceptible noise or vibration associated with the rotation The room's interior may be fully illuminated, or it may be darkened to exclude visual fixation stimuli Each of four chairs, facing the center of rotation and located four feet from center, was equipped with a biting board arrangement to restrict head tilts to the frontal plane, as shown in Fig 1 Potentiometers attached to the pivotal shafts were used to record head movements

Eye movements were recorded by the corneo retinal potential method Pairs of electrodes placed above and below one eye and at the outer canthus of each eye were used to record the vertical and horizontal components of nystagmus, respectively The potentiometer signals and the preamplified corneo-retinal potentials were fed through slip rings to a Sanborn recorder which was in an external room

Estimates of subjective effects were also obtained Subjects observed a small target light during head movements and estimated the intensity of subjective effects by assigning numbers on a 0 10 scale, for reactions ranging from absence of sensation to very intense sensation

Subjects were 22 officers and cadets in the naval aviation program, with apparently normal vestibular function and an age range of 20 to 24 years Of these men, 20 completed the experiment in two groups of 10 subjects

each Both groups received identical tests before and after the habituation series During the habituation series which lasted for several hours the room rotated at 7 5 RPM (45 deg/sec) Tests consisted of lateral head tilt toward the left shoulder and a return movement to upright position followed by a lateral tilt to the right shoulder and return movement to upright position Total angular displacement in each head movement was 45°, and this was accomplished in about 2 seconds Each head position was maintained until the nystagmus reaction was completed plus an additional 30 seconds

The only difference in the treatment of the two groups occurred in the habituation series In this series Group A the visual task group was required to solve problems of mechanical comprehension and spatial relations presented on a 10 × 10 luminous screen 3 feet from the subject Heights of letters in the reading material spanned 9 minutes of visual angle Subjects were told that their abilities under adverse circumstances were being tested and a competitive attitude prevailed Slides of interesting scenes were randomly introduced for diversion and to maintain interest Fingertip pushbuttons were provided with which subjects indicated multiple choice answers which were automatically scored [1]

Group B (dark unoccupied group) made all head movements during the habituation series with eyes closed and in a semi darkened portion of the room Head movements of this group were also signaled by the click of the slide projector although the projector and screen were not visible to these subjects Two subjects in this group were unable to complete the experiment due to rotation sickness thus of the 12 subjects who commenced the experiment under Group B conditions a total of 10 Group B subjects completed the experiment

The habituation series for both groups consisted of 100 head movement cycles i e 100 tilt and 100 return movements in the right quadrant while the SRR rotated counterclockwise at an angular velocity of 7 5 RPM Each head position was maintained for 20 seconds during habituation series except for 10 minute rest *periods* which were given after each series of 20 tilt return cycles During these periods subjects rested by means of a comfortable head support An on board observer insured that head movements were restricted to those specifically required

During all tests of nystagmus at the beginning and end of the day s run i e, before and after the habituation series nystagmus was recorded in darkness while the subject with eyes open (cf Guedry & Montague 1961 p 491) did mental arithmetic to avoid loss of nystagmus due to arousal factors (cf Collins 1962) Subjects were *also tested* at these times for the Coriolis oculogyral illusion (Graybiel et *al* 1961) Tests involving the same head movements were conducted also *with the room* stationary (static tests) before and

[1] The author is indebted to Mr Thomas Decker and Mr Gene Turnipseed who constructed the automatic scoring device and assisted in conducting the experiment and to the naval aviation officers and cadets who served as subjects

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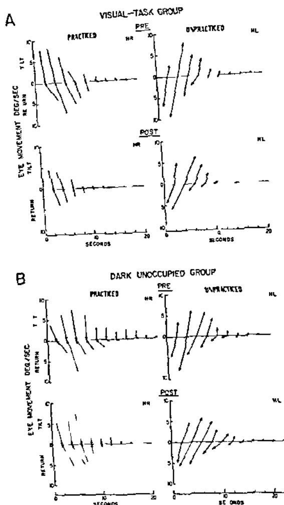


FIG 3 Vectorial representation of direction and magnitude of nystagmus at 2 sec intervals throughout the course of each reaction in the pre and post tests Length of the arrows indicates magnitude of the velocity of the slow phase of nystagmus direction of arrows indicates plane and direction of the nystagmus fast phase relative to the sagittal plane of the skull An arrow up and to the reader s right designates nystagmus with fast phase directed diagonally up and to the right of the subject s sagittal plane

The subjective data are based on the intensity ratings given by subjects For example it was assumed that an intensity rating of 4 during the pre tests and a rating of 2 during the post tests represented a response decline of 50 per cent Subjects were questioned after they gave their intensity ratings at the end of the day to check for consistency between verbal estimates and numerical indications of response declines In Group A, the average decline in subjective response was 76 per cent in the practiced quadrant and 11 per cent in the unpracticed quadrant In Group B average decline was 42

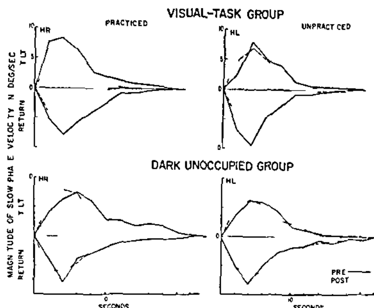


Fig. 2. Magnitude of slow phase velocity of nystagmus obtained by resolving records of the horizontal and vertical components of eye movements at 2 sec intervals throughout the course of the reactions. Solid and dashed lines indicate pre- and post-tests, respectively.

after the entire procedure just described to detect compensatory reactions which might have developed (cf. Guedry & Graybiel 1962).

In addition, when the SRR was started and stopped in tests before and after the habituation series, nystagmus was recorded from some of the subjects to determine whether or not there was any transfer of habituation from the series of head movements to the nystagmus occasioned by passive angular acceleration of the entire body.

RESULTS

Horizontal and vertical components of the nystagmus slow phase were measured throughout each subject's reaction in the several test trials. Records were divided into 2 second intervals; separate averages for the two components were obtained for each interval for each group. Vectorial resolution of these two components then provided a single vector representing the magnitude and direction of the average response for each 2 second interval throughout the reaction. Fig. 2 presents only the magnitudes of these vectors to facilitate visual comparisons of the response declines. Figs. 3 A and B show, by vectorial presentation, the magnitude and direction of the nystagmus slow phase throughout the course of the reaction in each group. In addition, the slow phase eye movement displacement throughout the course of each reaction was summed for each subject. Vectorial resolution of these total horizontal and vertical components was then obtained and magnitudes were averaged over subjects to permit calculation of per cent declines of nystagmus indicated in Table 1.

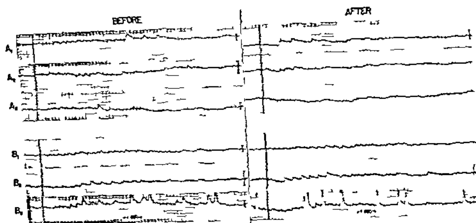


Fig 4 Sample records from six subjects showing the vertical nystagmus component produced by head return from right tilt before and after the habituation series Subjects A_1 A_2 and A_3 were from Group A (visual task group) and Subjects B_1 B_2 and B_3 were from Group B Calibration markers at right of each record represent 20 degrees of eye movement Vertical lines to left of each record mark onset of head movement

The differences in these two groups in regard to response declines are illustrated in Figs 2 3, and 4 Fig 4 presents nystagmus records from three subjects in each group

DISCUSSION

Although the average initial nystagmus response was slightly greater in Group B the pronounced differences between Groups A and B in regard to response declines, nausea and aftereffects are probably not attributable to initial differences in motion sickness susceptibility between the two groups Subjects were pilot candidates in the pre flight training program and were interviewed prior to the experiment in an attempt to match the groups in regard to susceptibility to motion sickness Moreover, the predominance of subjective effects during the post habituation static tests in Group A suggests that they were not merely a less susceptible group

The predominance of sickness in Group B during the habituation program was not anticipated However, in retrospect, the results in regard to vegetative symptoms agree with spontaneous comments from personnel engaged in Pensacola SRR experiments, namely, that heightened mental activity and interest in a task seem to suppress nausea and malaise Wendt (1951) has made similar comments In our experiment a sensory conflict was inevitable in any head movement whether vision was present [illegible] canal inflow would be antisynergic with otolith and [illegible] either case With vision permitted otolith [illegible] provide [illegible] with

TABLE 1 *Per cent change in nystagmus in tests before and after habituation series*

Minus and plus signs indicate decrements and increments, respectively

	Practiced quadrant		Unpracticed quadrant	
	Tilt	Return	Tilt	Return
Group A	−69	−59	+1	−18
Group B	−31	−18	+18	−2

per cent in the practiced quadrant and 14 per cent in the unpracticed quadrant

There was no evidence of a decline in nystagmus produced by the angular accelerations of the SRR, although this was not adequately investigated in this experiment Of seven subjects (5—Group A, and 2—Group B) who were tested in this manner, all exhibited strong nystagmus during the deceleration which ended the experiment

Salient features of the results of this experiment were as follows

1 The rotation tests before and after the habituation series indicated that Group A subjects all demonstrated a clear decline in nystagmus and in subjective effects in the practiced quadrant In contrast with the previous experiment (Guedry, *et al*, 1964), there were no exceptional subjects who failed to evidence a decline in the practiced quadrant In the unpracticed quadrant there was little response decline in nystagmus subjective results evidenced a little more response decline than did nystagmus in this quadrant

Those subjects whose habituation series was conducted in darkness Group B, showed little or no decline in nystagmus in the practiced or the unpracticed quadrant Subjective response declines indicated by this group were less than those indicated by Group A

2 Group A, the visual task group, was relatively free of motion sickness symptoms, three of ten subjects reported nausea which disappeared early in the habituation run None of these subjects vomited On the other hand six of twelve subjects in Group B were severely disturbed by motion sickness Two of these could not complete the experiment and four subjects vomited several times When nausea occurred, it usually persisted in Group B throughout the run

3 In the static tests after the habituation series, Group A reported subjective effects principally in the practiced quadrant Group B reported little or no effects in the subsequent static tests in either practiced or unpracticed quadrants These subjective effects in Group A appear indicative of the development of a compensatory reaction evidenced in other studies, but nystagmus did not provide direct evidence of compensatory reactions in the static tests

however, that here also nystagmus habituation in human subjects is influenced by a visual task. These experiments considered together leave little doubt that vision is an important factor in the habituation of vestibular nystagmus in human subjects, and the results are consistent with views expressed previously by Wendt (1936, 1951) and others.

This series of experiments on the SRR appears analogous to studies of adjustment to optical distortion of retinal images (Cohen & Held, 1960; Kohler, 1951). In these optical experiments proprioceptive and vestibular influx accompanying movements of the head and body would be normal, but the visual influx would be at variance with influx from these other systems. In these studies, as in those of Graybiel and others (Clark & Graybiel, 1961; Graybiel *et al.*, 1960, 1961; Guedry & Graybiel, 1962; Guedry *et al.*, 1964), neurovegetative symptoms and poor coordination occurred initially, but with continued exposure, undesirable and inappropriate reactions diminished. In both situations, return to a natural sensory environment was accompanied by a period of readjustment in which most of the undesirable effects reappeared.

Cohen & Held (1960) have demonstrated that active, as opposed to passive participation of subjects during exposure to bizarre combinations of visual and proprioceptive sensory influx is important in the adjustment they achieve. It seems likely that such a subtle condition, i.e., active as opposed to passive participation, may be important to a series decrement which may occur when visual stimulation suppresses vestibular nystagmus. It has been indicated that nystagmus and disturbance of equilibrium decline markedly in individuals who routinely encounter complex vestibular stimulation by virtue of daily occupation (Aschan, 1954; McCabe, 1960). Perhaps it is important that these individuals typically initiate the stimulus by their voluntary actions, that they would be endangered by false sensory data, that vision when available would be used actively to suppress nystagmus and apparent motion effects, and that the success or failure of the suppression would usually be comprehended immediately by the participant.

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ZUSAMMENFASSUNG

Zwanzig mannliche Versuchspersonen wurden einem Experiment im *Pensacola* Slow Rotation Room (SRR) unterworfen, wahrend er fur mehrere Stunden mit einer Geschwindigkeit von 45 grad/sec rotierte. Die Versuchspersonen verharrten unbeweglich (*relativ zum SRR*), ausgenommen wahrend Ubungsserien, die aus Kopfbewegungen bestanden und sich auf einen Quadranten einer Ebene beschrankten. Sehaufgaben wurden mit jeder Kopfbewegung einer Gruppe gestellt, eine andere

the voluntary head movements and only canal influx would be antisynergic with other sensory input.

In the present experiment the introduction of a visual task which required voluntary oculomotor control had a definite influence on nystagmus habituation. The average response decline obtained in the present experiment in the visual task group was slightly greater and was more consistent than the declines obtained in the previous experiment (Guedry *et al.* 1964) in which subjects experienced *similar habituation procedures with vision permitted* but without visual tasks being required. These conditions are to be contrasted also with those experiments in which illumination was introduced during repetitive stimulation of restrained animals (Crampton 1962, Proctor & Fernandez 1963). Species differences in reactions to restraint may be one of several subtle factors contributing to variability of results in this line of experimentation (cf. Wendt's comments on "animal hypnosis" of restraint, 1936, 1951, p. 1215), but in any case it is difficult to assess the extent to which voluntary oculomotor control interacts with vestibular effects in animals.

Because subjects in the present experiment were tested in the beginning and at the end of the day using mental arithmetic to prevent nystagmus loss due to loss of arousal, it is likely that a large portion of the reductions observed are primarily attributable to some process other than the loss of arousal.

In a series of experiments involving repetitive elicitation of the Coriolis vestibular reaction, clear evidence has been obtained for the development of conditioned compensatory reactions (Graybiel *et al.* 1961, Guedry & Graybiel 1962, Guedry *et al.* 1964) which counteract inappropriate patterns of sensory influx. The present experiment suggests that vision is conducive to the development of this compensatory reaction, although it is likely that a pattern of exteroceptive and interoceptive stimuli is involved in releasing the reaction. It is to be noted, however, that although vision and the voluntary aspect of the movement may facilitate the conditioning process, they are not necessary to the elicitation of the compensatory response once it has been developed (Guedry & Graybiel 1962). Furthermore, the differences between the practiced and unpracticed quadrant in Group B suggest that some factor other than vision, possibly but not necessarily arousal, was influencing results.

The influence of visual oculomotor control on nystagmus habituation may be greater with the unnatural sensory influx of the voluntarily initiated Coriolis vestibular reaction than with other forms of vestibular stimulation. The presence of the information garnered from the voluntary aspect of the movement, the sensory information from the otoliths, proprioceptors, *et cetera* may be necessary along with visual suppression for the development of the compensatory nystagmus. Some of these elements would not be present in simple vestibular stimulation involving only passive angular acceleration of the subject about a fixed vertical axis. A more recent experiment (Guedry 1964) employing simple passive vestibular stimulation has demonstrated

however that here also nystagmus habituation in human subjects is influenced by a visual task. These experiments considered together leave little doubt that vision is an important factor in the habituation of vestibular nystagmus in human subjects, and the results are consistent with views expressed previously by Wendt (1936, 1951) and others.

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ZUSAMMENFASSUNG

Zwanzig männliche Versuchspersonen wurden einem Experiment im Pensacola Slow Rotation Room (SRR) *unterworfen*, während er für mehrere Stunden mit einer Geschwindigkeit von 30 *grad/sec* rotierte. Die Versuchspersonen verharrten unbeweglich (relativ zum SRR) ausgenommen während Übungsserien, die *aus Kopf*bewegungen bestanden *und sich* auf einen Quadranten einer *Ebene beschränkten*. Sehaufgaben *wurden mit* jeder Kopfbe*wegung* einer Gruppe gestellt, eine andere

Gruppe führte alle Kopfbewegungen der Übungsserien im Dunkeln aus. Versuche im Dunkeln vor und nach den Übungsserien zeigten eine ausgesprochene Verringerung des Nystagmus und subjektive Effekte im Übungsquadranten nur in der „Schauf gaben"-Gruppe. Die andere Gruppe zeigte weder in dem geübten noch in dem ungeübten Quadranten eine Verringerung des Nystagmus. Diese und weitere soeben vollendete Versuche beweisen, dass Sehen ein wichtiger Faktor in der Gewöhnung menschlicher Versuchspersonen an vestibuläre Reize sein kann.

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Gruppe führte alle Kopfbewegungen der Übungsserien im Dunkeln aus Versuche im Dunkeln vor und nach den Übungsserien zeigten eine ausgesprochene Verringerung des Nystagmus und subjektive Effekte im Übungsquadranten nur in der „Schaufgaben"-Gruppe Die andere Gruppe zeigte weder in dem geübten noch in dem ungeübten Quadranten eine Verringerung des Nystagmus Diese und weitere soeben vollendete Versuche beweisen, dass Sehen ein wichtiger Faktor in der Gewöhnung menschlicher Versuchspersonen an vestibuläre Reize sein kann

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changes formerly attributed to postmortem autolysis are actually artifacts of specimen preparation

Recently Schuknecht (1964) pointed out that in some instances clinical functional tests and routine histopathological findings do not conform and suggested that a different approach be made to these problems Electron microscopy may not be the final answer to such cases but as we demonstrate in the present investigation it may be able to resolve some unanswered questions

MATERIALS AND METHODS

The ages of the eight Caucasian patients with no known histories of middle or inner ear problems ranged from 17 to 77 In two cases dry ice was introduced deep into the external auditory meatus to lower the temperature of the inner ear In three other cases 1% phosphate buffered osmium (Millonig 1961) was introduced directly into the vestibule with a spinal needle through the oval window The postmortem time ranged from two to four hours before fixation

The petrous bone was originally removed by a bone plug method but its large bulk presented problems A simpler method was adopted of fracturing the temporal bone on the long axis of the middle ear cavity with a strong bone cutter starting from the posterior lateral margin of the subarcuate eminence and ending in the region of the internal carotid artery Immediately after the block was removed from the skull the round window was opened the oval window was enlarged and the fixative was gently agitated through the oval window allowing osmium to pass through the entire membranous labyrinth Between intermittent fluid perfusions, the temporal bone was trimmed very rapidly with bone cutting forceps and a rongeur and the apex of the cochlea was drilled open to facilitate further fluid exchange

With the specimen immersed in 70% alcohol the vestibular sensory epithelia were dissected out and the scala tympani of the basal turn was opened along the spiral direction to facilitate embedding in Epon (Luft 1961) The entire cochlea was embedded in a clear gelatin capsule (adequate size) slightly collapsed to accommodate the specimen The polymerized specimen was clamped in a small vise and after careful orientation of the specimen, a jeweler s string saw was used to make deep grooves in the otic capsule without entering the membranous part which was easily identifiable by its osmium staining The string saw was preferred to a fast moving circular saw for its easy control A gentle tap on a razor blade placed in the saw groove yielded a clean shiny separation surface with minimal damage to the membranous labyrinth The halved cochlea was bisected repeatedly each turn separated and the pieces orientated [illegible] blanks for horizontal or vertical planes through

FINE MORPHOLOGY OF THE SENSORY CELLS IN THE ORGAN OF CORTI OF MAN

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The morphological characteristics of the sensory cells and neural elements in the human cochlea were studied with the electron microscope. The hairs of the outer sensory cells were arranged in a W form with at least six rows. The basal body or diplosomes were found in the cuticle free zone in the sensory cells. The subcuticular zones of the outer sensory cells frequently contained numerous osmiophilic inclusions. Two types of nerve endings, dendrites and axons, were observed below both the outer and inner sensory cells. The external spiral bundle was large and composed of numerous, closely packed nerve fibers. In specimens from older patients there were some evidences of nerve ending degeneration at the base of hair cells.

The findings in the human were compared with the normal and post mortem series of squirrel monkeys. When human specimens were fixed within a few hours of death, the ultrastructure of the inner ear could be investigated effectively, as is seen in the present study.

INTRODUCTION

Little information is available on the fine structure of the normal human labyrinth. The investigation of ultrastructure in the human has been delayed, because it is usually not possible to acquire the human inner ear soon after death, and autolytic changes were presumed to occur rapidly. Some human pathological specimens have been obtained at the time of surgery, for example, studies have been made on the vestibular sense organs of patients with Ménière's disease (*Pietrantoni & Iurato*, 1960, Litton & Lawrence, 1961, Ireland & Farkashidy 1963, Friedmann, Cawthorne, McLay & Bird, 1963).

The possibility of obtaining valuable information from the human postmortem inner ear is indicated by the preliminary electron microscopic data of autolytic changes in the guinea pig (Wersäll, Kimura & Lundquist). Ito (1962), in his electron microscopic postmortem study on liver, kidney, and stomach, stated that some structural alterations occur slowly, and such

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FIG 1 An outer sensory cell demonstrating numerous osmiophilic inclusions and long endoplasmic reticula in its subcuticular zone A basal body is seen on the left at one of the cuticle free areas Basal turn Age 60 The line in each of the following figures indicates a length of one micron

opaque This membranous structure which is another form of the endoplasmic reticulum may correspond to the Hensen body as described in lower mammals by Engstrom & Wersall (1958) and Spoendlin (1957)

The hairs of the outer sensory cells were arranged in a W throughout the cochlea with the base of the W facing the spiral ligament (Figs 3 A, 3 B) The number of hairs varied in the different turns within each turn itself and in different specimens In the basal turn of the human organ of Corti the number ranged from 120 to 148 in the limited number of cells studied while in the apex the number was between 46 and 80 Six to seven rows of hairs were present, the tallest rows were at the periphery with the height decreasing in the inner rows (Figs 4 A 4 B) where the number of hairs were also reduced The tallest hairs were found in the out... few rows of the hairs at the base of the W

Some hair rootlets pierced the cuticular plate and extended f... distance into the cytoplasm (Fig 5 A) Occasionally dark granular str... ran from the cuticular plate deep into the cytoplasm accompanie... numerous short tubular structures mitochondria and granules ... previous reports on lower mammals the outer edge of the c...

For control studies of postmortem change, four squirrel monkeys were sacrificed and their inner ears fixed at varying times after death. One cochlea from each monkey was fixed immediately, while the other was left intact in the skull at room temperature (23°C) for one, three, and five hours. In the fourth monkey osmium was injected into the vestibule through the oval window one hour after death, after which the entire cochlea was left at room temperature for four more hours before removal and final fixation.

The specimens were cut with an LKB ultratome, stained with alcoholic uranyl acetate or lead hydroxide (Karnovsky, 1961) and photographed with a Siemens Elmiskop I with the initial magnifications ranging from 1000× to 30,000×.

FINDINGS

Cooling of the inner ear was found to be of some benefit in slowing postmortem changes, but the immediate injection of ice cold 1% phosphate buffered osmium tetroxide through the oval window yielded the best results.

The postmortem experiments on squirrel monkeys indicated that little worthwhile information could be obtained from the sensory cell area of the specimen fixed five hours after death. However, the cochlea left intact in the skull and fixed through the oval window one hour after death which remained at room temperature for four additional hours, showed remarkably good preservation.

A striking feature in the human was the presence of numerous, large dark, granular inclusions in the apical zone of the cytoplasm of sensory cells (Figs. 1, 4 A, 5 A, 5 B, 7 A), pillar cells, Hensen cells, Deiters cells, and sulcus cells. A few of these inclusions were also found in the infranuclear zone in outer sensory cells. In the Deiters cells, they were found in the region adjacent to the basal part of the sensory cell and in the slender protoplasmic extensions which lead toward the reticular lamina (Fig. 4 A). These dark inclusions varied in size, shape, and content. The majority of the inclusions had a clear outer membrane within which was a large, oval opaque substance and numerous small granules. Lipid droplet inclusions and inclusions of numerous fine granules with occasional larger dark granules, have also been observed.

In man it was very common to find a long tortuous, granular endoplasmic reticulum in the vicinity of the cuticular plate of outer sensory cells (Figs. 1, 4 A). The similar endoplasmic reticulum in the supranuclear zone of Deiters cells was more pronounced, with a concentric or interweaving form (Figs. 2 A, 8 A). Large, concentrically arranged membranous structures were occasionally found in the supranuclear zone of the outer sensory cells, adjoined by several similar membranous segments (Fig. 2 B). The inner circle and the area between the double membranes remained less



FIG. 3 A. A cross section through the hairs of five outer human sensory cells showing the W arrangement. The groups of hairs to the left are cut closer to the reticular lamina (R) and consequently show *more* hairs. One hundred forty two hairs are found in the middle sensory cell. Human, basal turn.

FIG. 3 B. Electron micrograph showing the three rows of outer sensory cells enclosed by reticular membranes. Note the absence of two sensory cells in the *third* row. Dark inclusions are *seen* both in the reticular plates and sensory cells. An arrow points toward the spiral ligament. Basal turn. *Age 63*

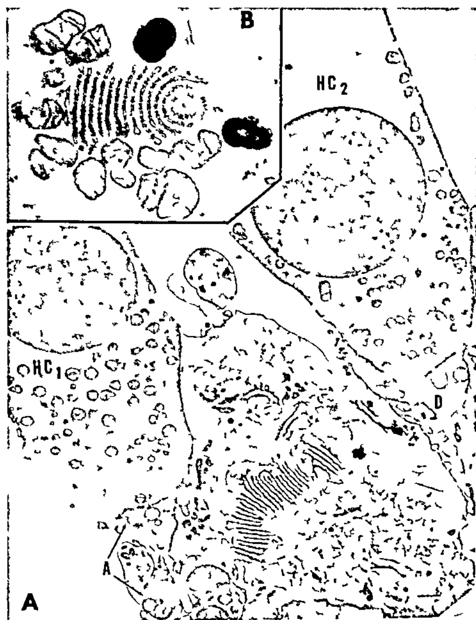


Fig. 2 A. Electron micrograph showing the general morphological arrangement of outer sensory cells (HC1 first row, HC2 second row), nerve endings and Deiters cells. Note the two types of nerve endings: axon terminal (A) and dendritic terminal (D). The bulging at the basal part of the outer sensory cell (HC) is probably due to postmortem change. The Deiters cell contains a prominent endoplasmic reticulum. Basal turn. Age 60.
Fig. 2 B. Electron micrograph showing the lamellar arrangement of endoplasmic reticulum surrounded by mitochondria and dark inclusions taken from the apical zone of an outer sensory cell.

human sensory cell is missing in many parts (Figs. 1, 4 A). A short electron dense layer, tubules and mitochondria were found close to the plasma membrane in these cuticle free zones. There was frequently a basal body located at one of the cuticle free zones toward the Hensen cell side (Fig. 1). One atypical large stereocilium with multiple rootlets (Fig. 3 B

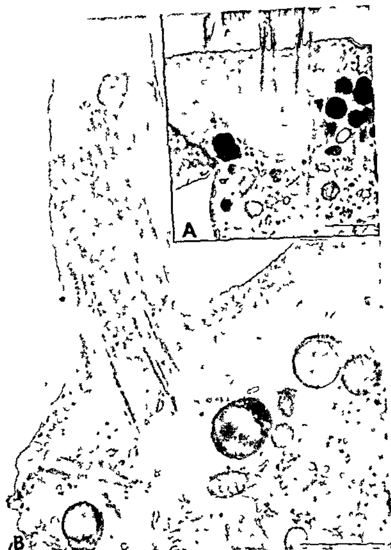


Fig 5 A Electron micrograph demonstrating an extension of the hair rootlet deep into the cytoplasm Human basal turn

Fig 5 B Electron micrograph of an outer sensory cell showing a large stereocilium with multiple rootlets adjacent to the area of the diplosome Note mitochondrion within the cilium Apical turn Age 60

was found next to what appeared to be a diplosome in a section of an outer sensory cell No kinocilium was ever seen

Nerve endings were not numerous below outer sensory cells at the basal turn even when examined from three different angles At least two dif

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Fig 6 A Electron micrograph showing an axon terminal of the olivo-cochlear bundle (A) and dendrite terminal (D) abutting on an outer sensory cell (HC) An accessory membrane is seen in the sensory cell at the area adjacent to the axon terminal Basal turn Age 63



Fig. 4 A. Electron micrograph showing the decreasing height of the hairs in succeeding inner rows. Note the cuticle free zones and the deep extension of the cuticle with its associated aggregation of mitochondria and dark inclusions. The large inclusions are also seen in the adjacent Deiters cell process. An arrow indicates the direction of the spiral ligament. Basal turn. Age 0

Fig. 4 B. Electron micrograph showing the relative heights of hairs in outer sensory cells sectioned vertically in the spiral direction. The middle hair cell demonstrates the taller hairs at the base of the W. The hairs of the cell to the right are a little distance within the W while the hair cell to the left shows a still deeper portion as is indicated by the size of the cuticular plate. Note the aggregations of mitochondria and dark inclusions in the subcuticular zones and the close relationship between mitochondria and peripheral membranes. Basal turn. Age 63

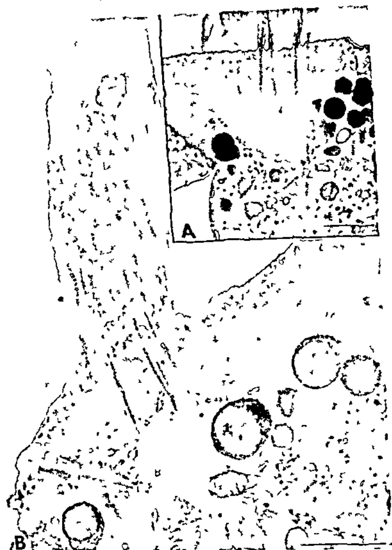


Fig. 5 A. Electron micrograph demonstrating an extension of the hair rootlet deep into the cytoplasm. Human basal turn.
Fig. B. Electron micrograph of an outer sensory cell showing a large stereocilium with multiple rootlets adjacent to the area of the diplosome. Note mitochondrion within the cilium. Apical turn. Age 60.

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Fig. 6 A. Electron micrograph showing an axon terminal of the olivo-cochlear bundle (A) and dendritic terminal (D) abutting on an outer sensory cell (HC). An accessory membrane is seen in the sensory cell at the area adjacent to the axon terminal. Basal turn. Age 63.

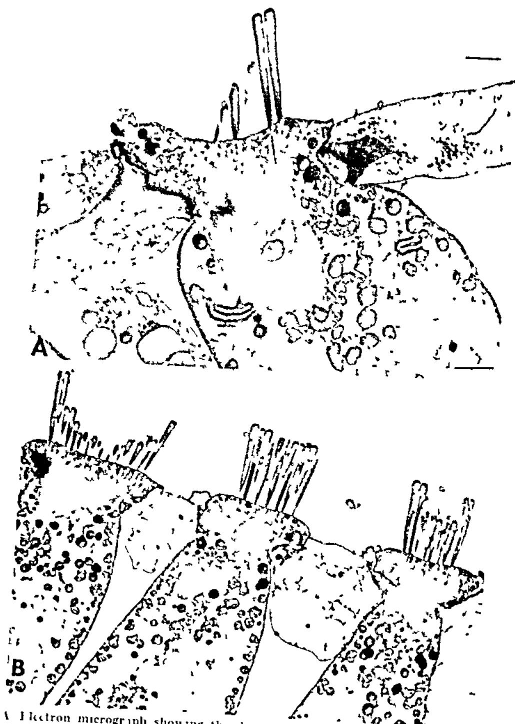


Fig. 4 A. Electron micrograph showing the decreasing height of the hairs in succeeding inner rows. Note the cuticle free zones and the deep extension of the cuticle with its associated aggregation of mitochondria and dark inclusions. The large inclusions are also seen in the adjacent Deiters cell process. An arrow indicates the direction of the spiral ligament. Basal turn. Age 50.

Fig. 4 B. Electron micrograph showing the relative heights of hairs in outer sensory cells sectioned vertically in the spiral direction. The middle hair cell demonstrates the taller hairs at the base of the W. The hairs of the cell to the right are a little distance within the W while the hair cell to the left shows a still deeper portion as is indicated by the size of the cuticular plate. Note the aggregations of mitochondria and dark inclusions in the subcuticular zones and the close relationship between mitochondria and peripheral membranes. Basal turn. Age 63.



Fig. 8A. Electron micrograph of the *external spiral bundle* demonstrating the numerous nerve fibers between the *Deiters cells* (D). Note pronounced endoplasmic reticula in the Deiters cells. HC *outer sensory cells*. Human, second turn.
Fig. 8B. Electron micrograph of the external *spiral bundle* demonstrating the short thick plasma membranes of the *nerve fibers*. A few thickenings without vesicles may be desmosomes. A large *axon process* is located at the lower right corner. Human, basal turn.

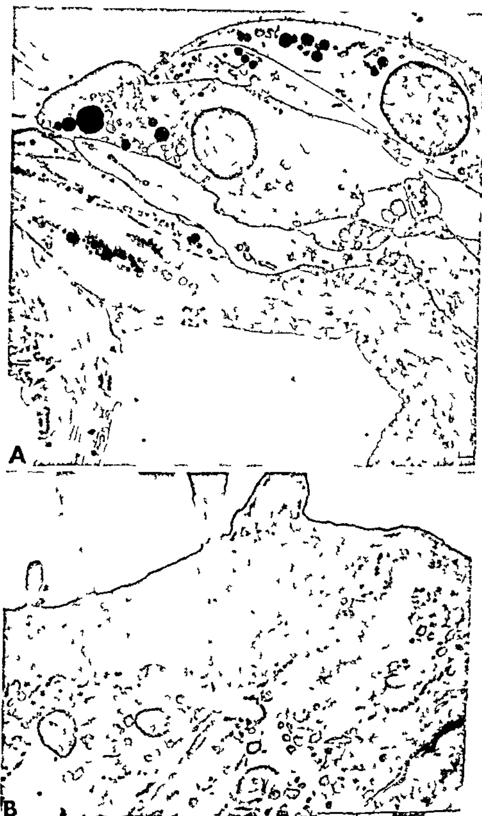


Fig. B. Electron micrograph showing a basal body and a centriole which extends closer to the rootlet in subsequent sections of the inner sensory cell. Note the rootlets penetrating the cuticular plate with their aggregations of tubules and granules. *Basal turn.* Age 50.



Fig. 8 A. Electron micrograph of the external spiral bundle demonstrating the numerous nerve fibers between the Deiters cells (D). Note pronounced endoplasmic reticula in the Deiters cells. HC (outer sensory cell). Human second turn.

Fig. 8 B. Electron micrograph of the external spiral bundle demonstrating the short thick plasma membranes of the nerve fibers. A few thickenings without vesicles may be desmosomes. A large axon process is located at the lower right corner. Human basal turn.

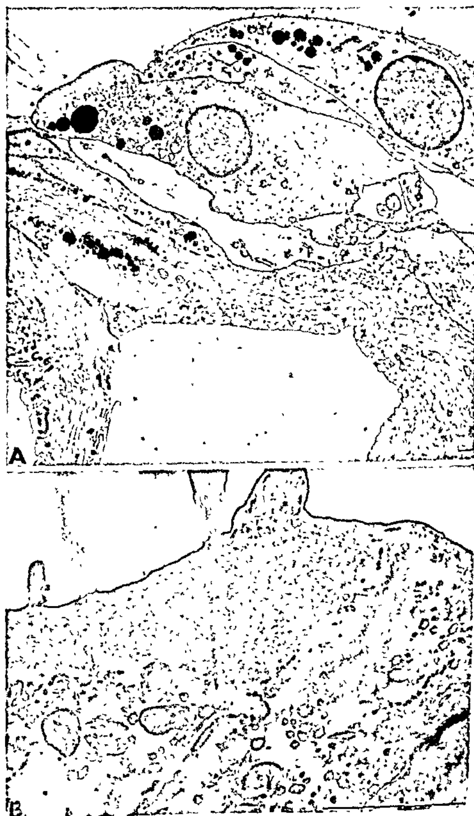


Fig. 7 B Electron micrograph showing a basal body, and a centriole which extends closer to the rootlet in subsequent sections of the inner sensory cell Note the rootlets penetrating the cuticular plate, with their aggregations of tubules and granules. Basal turn Age 50

DISCUSSION

The granular inclusions, many of which are found on the endolymph surface of the sensory cells of the human organ of Corti (Figs 1, 7 A), are also seen occasionally in the subcuticular zone of the sensory cells in bat, guinea pig, cat, and squirrel monkey. Similar inclusions are found in the vestibular sensory cells of the human (Ireland & Farkashidy, 1963, Friedmann *et al*, 1963) Their nature is not clear, although they are presumed to be pigment In experimental animals subjected to acoustic trauma, these inclusions have been observed to increase in number (Spoendlin, 1958) and to accumulate more osmiophilic material (Engström & Ades, 1960) Our observations indicate that the number of inclusions in new-born bats and young squirrel monkeys is less than in mature specimens of the same species In man the number of inclusions varied considerably among the different specimens, for example, the specimens aged 71 and 77 showed no more inclusions that that aged 17 The varying number and size of inclusions may possibly indicate exposure to trauma, changes in the cochlear fluid and other physiological conditions in the inner ear Since the squirrel monkey organ of Corti, kept as long as five hours at room temperature after sacrifice, does not show a significant increase in the number of such granular masses, they are probably not caused by the autolytic process

Six to seven rows of hairs are found in a W arrangement on the cuticle of the human outer sensory cell (Fig 3 A) In the bat, guinea pig, and cat, there are three rows of hairs in the W form while five to six rows are observed in the outer sensory cells of the squirrel monkey Similar findings in the human were previously reported by both Held (1926) and Kolmer (1927) According to Kolmer, the hairs on an individual outer sensory cell are taller away from the modiolus, and a flagellum and diplosome are found closely associated at the base of the W Our observations indicate that the taller hairs are located in the peripheral rows of the W, with the height of the hairs decreasing in the subsequent inner rows (Figs 4 A, 4 B) The tops of the short hairs in the innermost rows of the W are probably not embedded in the tectorial membrane proper

Although we have been unable to find a flagellum or a kinocilium in the sensory cells of the cochlea, we have found a basal body in the cuticle free zone toward the Hensen cell (Figs 1, 5 B, 7 B) Basal bodies were previously described in the outer sensory cells of the guinea pig with the electron microscope (Flock, Kimura, Lundquist & Wersäll, 1962) Using phase contrast microscopy, Engström, Ades & Hawkins (1962) reported the absence of a flagellum in the guinea pig, but also noted a basal body in the same region Friedmann (1962) reported observing a kinocilium in the fowl otocyst In human sensory cells, we occasionally found a centriole at an obtuse angle to the basal body (Figs 5 B, 7 B) Similar arrangements of basal bodies and centrioles or diplosomes were sometimes seen in the



Fig. 9A. Electron micrograph showing axon (A) and dendrite (D) processes synapsing (arrow) in the external spiral bundle. There is a greater concentration of vesicles on the axon side. Note many large neurofilaments and mitochondria arranged at the periphery of the axon process. Human.

Fig. 9B. Electron micrograph showing two large granular masses among the nerve fibers in the external spiral bundle. The short thick plasma membranes of the nerve fibers can be seen at top and bottom. Note a long protoplasmic extension of the Deiters cell into the bundle. Age 60.

although the possibility that they may be remnants of degenerating nerve fibers cannot be ruled out. They were more common in specimens taken from older individuals. Similar inclusions were also observed in the pillar cell at the area adjacent to the tunnel spiral bundle. These inclusions were distinctly different from those seen on the cell surface of the organ of Corti.

the basal turn Held (1926) reported that the number of hairs per human outer sensory cell of the basal turn was more than 100 in the middle turn 67 to 83 and 63 to 65 at the apex We find more hairs in a human sensory cell in the corresponding turns than was previously described by Held The functional significance of the number size, shape, and height of the hairs and the angle of the W on the cuticular plate is not clear

Retzius (1884) and Bloom & Fawcett (1962) reported that there are three rows of outer sensory cells in the basal turn with the irregular addition of a fourth row in the middle turn and of a fifth row at the apical turn in both young and adult human Our study revealed that the human outer sensory cells are arranged in three rows at the lower basal turn (Fig 3 B) The sensory cells are not organized in an orderly manner in all rows in the cochlea This morphological variation will make it more difficult to determine the diffuse degeneration of sensory cells in man

Human sensory cells have two types of nerve endings (Figs 6 A, 6 B) as are found in small mammals axonal terminals and dendritic endings Nerve section experiments on the guinea pig (Kimura & Wersall 1962), the rat (Iurato 1962), the chinchilla (Smith & Rasmussen 1963), and the cat (Spoendlin & Gacek 1963), have proven that the large vesiculated nerve endings are the axon terminals of the olivo cochlear bundle Gacek (1961) demonstrated the distribution of the efferent olivo cochlear bundle in the areas of the spiral ganglia and osseous spiral lamina in dissected specimens of the human cochlea The synaptic zones between the axon and dendrite terminals below the sensory cells are unusual (Fig 6 B) These synapses have not been observed in lower mammals to our knowledge Desmosome like areas are frequently seen between two axon terminals below the outer sensory cells of man and normal squirrel monkeys In human specimens some of the electron dense areas at the plasma membranes of nerve terminals and both tunnel and external spiral bundles appear to be desmosomes The morphological differences between presumed desmosomes and synapses are shown in figures 8 B and 9 A Desmosomes have been previously described between the dendrite processes in the cerebellum and between axon and dendrite processes in the mammalian spinal cord by Grey (1961 and 1963)

In the human the external spiral bundle is often composed of numerous closely packed nerve fibers (Fig 8 A) contrary to the lower mammals where the nerve fibers often pass independently among the Deiters cells Consequently there are more synaptic areas demonstrated between the axonal and dendritic nerve fibers (Fig 9 A) It can also be inferred from the large bundle that some of these fibers travel for a long distance The enlargements of the axons within the external spiral bundle (Fig 8 B) appear similar to the axonal terminals on the hair cells Smith (1961) has described similar enlargements on the nerve fibers lying below the inner hair cells of the guinea pig

One of the most interesting findings in human material is the number of



Fig. 10. Electron micrograph showing basal portions of outer sensory cells (HC) which lack nerve endings except for one dendrite terminal D. The spaces below the sensory cell on the right are filled with a fine granular precipitate probably indicating degeneration of nerve endings. Human, lower basal turn.

cochlear and vestibular sensory cells of the guinea pig, in the retinal rods (Tokuyasu & Yamada 1959), distal hypophysis (Barnes 1961) and other areas. Engström *et al.* (1962) suggested that the basal body with its associated mitochondria, membranes and granules could be the essential excitable structure in the sensory cell. The centrioles are, however, commonly found in other epithelial linings, such as pillar cells, Hensen cells, border cells, and Boettcher cells close to the endolymph surface. It is interesting to note that the basal body and centrioles are just as resistant to autolytic processes as the synaptic bar, synaptic membrane and synaptic vesicles which are still identifiable a few hours after death.

The hairs of an outer sensory cell vary in number within each turn and from specimen to specimen. There are generally less in the apical than in

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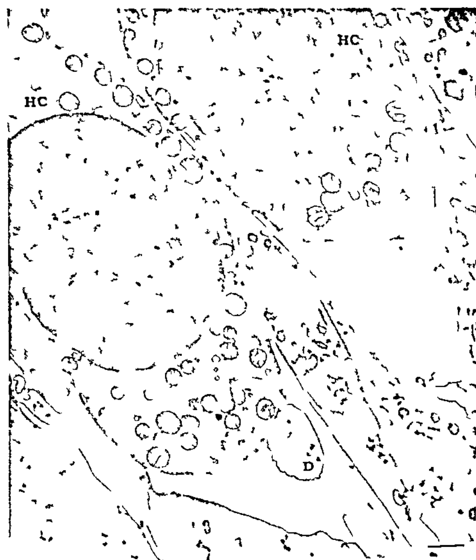


Fig. 10. Electron micrograph [illegible] of outer sensory cell (HC). [illegible] nerve endings except for one [illegible] (D). [illegible] cells on the right are full [illegible] with a fine granular precipitate [illegible] degeneration of nerve endings. [illegible]

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nerve endings below the outer sensory cells. In the basal turn the number is not large and is even smaller than in the guinea pig (see Fig. 14, Smith & Sjostrand 1961). A factor to be considered is the degeneration of nerve endings. More information is needed about the number of these nerve endings at upper and lower turns, especially of young individuals.

In postmortem specimens the sensory cells frequently detach from the Deiters cell cups creating blank spaces which may be interpreted as representing nerve degeneration, that is, that the space was previously occupied by a nerve ending. The same phenomena are seen in the postmortem series of squirrel monkeys. This finding is less common in better fixed human specimens. Figure 10 shows what seems to be degeneration of the nerve endings in the basal turn supported by the fact that granular material is present in the Deiters cup and there are no traces of plasma membranes even at higher magnifications. The space existing below the other outer hair cell is free of granular material and makes it doubtful that nerve endings have degenerated. It is possible that this degeneration is related to presbycusis. Present findings do not indicate, however, that nerve endings degenerate earlier than sensory cells in presbycusis. In some areas we found the sensory cells absent with nerve ending-like structures or nerve fibers still situated on the Deiters cells.

ZUSAMMENFASSUNG

Die morphologischen Einzelheiten der Haarzellen und ihrer Nervendigungen in der menschlichen Cochlea wurden elektronenmikroskopisch untersucht. Die Befunde am Menschen wurden mit normalen sowie postmortal veränderten Schnecken des Affen verglichen. Menschliche Gewebe, die innerhalb einiger Stunden nach dem Tode fixiert wurden, sind für elektronenmikroskopische Untersuchung geeignet.

ACKNOWLEDGEMENTS

We acknowledge the invaluable assistance of Miss Dency R. Baldwin and we are also grateful for the assistance received from Mr. Albert Dean Jefferson in procuring the temporal bones.

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VESTIBULAR RESPONSE TO SOUND SINGLE UNIT RECORDING FROM THE VESTIBULAR NERVE IN FENESTRATED DEAF MICE (Df/Df)

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Deaf mice of the Df/Df strain have degenerated cochleas but histologically normal vestibular structures After fenestration of the horizontal semicircular canal tones and clicks were delivered to the fenestrated ears through the external auditory canal using a closed sound system Single units of the vestibular nerve were picked out by tungsten microelectrodes Single unit responses were obtained only in fenestrated animals and only for frequencies from 80 to 1200 cycles per second Threshold was best for 1500 cycles per second and was at 78 db re 0.0002 dynes/cm Click responses were also obtained Some units with the spontaneous activity were driven by tone bursts others were inhibited Spontaneous activity was present in single units of non fenestrated mice but was not altered by tones or clicks and no units were driven by either type of sound stimulus The mode of vestibular endorgan stimulation and unit patterns are discussed in light of the present experiments

Deaf mice strain Df Df with degenerated cochleas and normal vestibular apparatus were fenestrated in their lateral semicircular canals and stimulated with sound Single unit recordings were made from the vestibular nerve using tungsten microelectrodes (the vestibular and cochlear nerves are separate in the mouse) Stimulating sounds were pure tones and clicks It was possible to obtain vestibular single units driven in response to sound stimulation This electrophysiologic evidence of the Tullio phenomenon may possibly provide another method to study the vestibular system

Since Tullio's observation (1938) about thirty five years ago of the head movements of pigeons when stimulated by sound after fenestration of the semicircular canal several reports have been made of physiological investigations of the labyrinth by this method and the possible bearing of the findings on the phylogenetic development of the hearing organ has been discussed The vestibular apparatus is known to be much older phylogenetically than the cochlear apparatus

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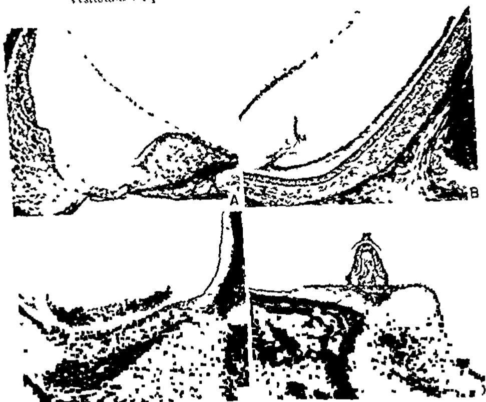


Fig 1 Labyrinth of the Df/Df mouse No 300 *A* Cochlea *B* saccular macula *C* utricular macula *D* crista 200

to a mammalian form The cochlear atrophy makes unnecessary an operative destruction of the hearing part of the inner ear The mouse has a further advantage in such an experiment because the cochlear and vestibular nerves are clearly separate

METHOD

The semicircular canals of mice are located posteriorly above the tympanic annulus They are approached by incising the skin above the pinna and cutting the muscles from the occipital bone The temporal and occipital bones in this area are separated by a very thin suture line The lateral semicircular canal can easily be identified and the fenestration made near its ampullary end using a micro drill with very fine edges Attempts are made to place the fenestra close to the ampulla making it also as large as possible The middle ear is thus kept intact with a normal functioning ossicular chain and tympanic membrane The histological appearance of the fenestra is shown in Figs 2*a* and 2*b*

The observation that microphonics (crista effect) can be recorded from fish has been used to try to explain hearing by fish. The cupulas are supposed to be stimulated by sound waves. Lowenstein & Roberts (1951) using an elasmobranch obtained microphonics from the isolated labyrinth but could not demonstrate any single unit activity with stimulation by sound. With vibratory stimuli he was able to get single unit recordings from the ampullary nerves. By placing a telephone receiver on the operating table he got single unit responses to the vibratory stimulus over the range of 10 to 120 cps. The spike amplitudes became larger as the vibratory force increased. He ascribes this effect to summation and recruitment.

In studying the Tullio phenomenon pigeons have been employed more than other laboratory subjects because it is moderately easy to remove the lagena (hearing endorgan) and to fenestrate the various semicircular canals. In Huizinga's review of the literature (1962) the various aspects of the crista effect are discussed. His review includes mostly the work done in his laboratory. He discusses in detail the haircell theory and the superposition effect. De Vries & Bleaker (1947) and de Vries *et al.* (1952) working in the laboratory *of Huizinga demonstrated that the microphonic effect was* obtainable from the fenestrated ampulla of the pigeon. They obtained responses from 300 to 2200 cycles per second with the most sensitive range being from 500 to 1000 cycles per second. They regarded the activity of the crista, that is the crista effect, to be similar to the cochlear microphonics. They reported that the crista microphonic effect had an input output curve similar to the auditory cochlear potentials and that after a maximum response the crista microphonic effect diminished. However, after a period of rest *the original maximum responses could again be obtained*. Van Eyck (1951, 1955) in his extensive investigations of fenestrated pigeons recorded the electrical phenomena at the new fenestra. He found the range of the crista microphonics to be from 100 to 3000 cycles per second, the optimum frequency being 900 cycles per second. *He could not, however, demonstrate* any loading effect. Van Eyck recorded also a gross nerve action potential in response to a click. This did not change with reversal of polarity of the click and the latency of the response depended on where and which of the canals was fenestrated.

MATERIAL

In the present experiments deaf mice of the strain classified by Deol as Df Df were employed. They were originally obtained from him in England (1956) and have been propagated in our animal quarters. The lesions in the inner ear as far as can be determined by histologic study are limited to the cochlea. In the adult is seen a complete atrophy of the organ of Corti and of the spiral ganglion and nerve fibers (Fig. 1 A). The entire vestibular apparatus including the saccule is histologically normal (Fig. 1 B, C, D).

The use of this animal has extended the study of the Tullio phenomenon



Fig. 3. *1* Vestibular nerve, *2* cochlear nerve, *3* subarcuate fossa (the paraflocculus is removed), *4* anterior semicircular canal.

To expose the vestibular nerve, the calvarium over the cerebellum is removed and enough of the cerebellum aspirated to expose the anterior semicircular canal with the paraflocculus in the subarcuate fossa. The paraflocculus is aspirated and the medulla retracted medially exposing the vestibular nerve cephalad and the cochlear nerve caudad (Fig. 3). Single unit recordings could be obtained only from the vestibular nerve. Recordings could not be obtained from any other place. The saccular nerve runs with the cochlear nerve and no responses were obtained from it.

At the end of each experiment the animals were perfused according to a technique described by von Békésy *et al.* (1961) and the heads were decalcified, embedded in celloidin and sectioned serially at 14 micra thickness. Each fifth section was stained for histologic study.

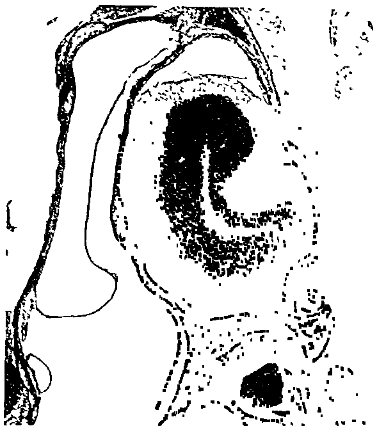


Fig. 2a. Fenestrated lateral semicircular canal. Df/Df. No. 1107. ×40.



Fig. 2b. Same as 2a. ×250. Membranous labyrinth intact.



Fig. 3. 1 Vestibular nerve 2 cochlear nerve 3 subarcuate fossa (the paraflocculus is removed) 4 anterior semicircular canal

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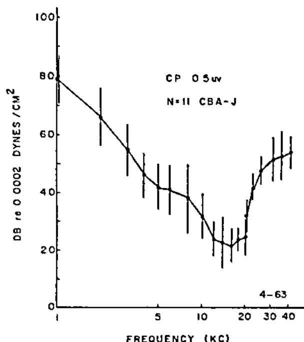


Fig. 4. Mean 0.5 microvolt cochlear potential of eleven CBA-J mice.

RECORDING TECHNIQUE

The pure tone frequencies were obtained from a Hewlett-Packard oscillator, type 201-C, amplified by a 75 watt MacIntosh amplifier, and attenuated by a Hewlett Packard attenuator, type 350 A. The sound was delivered from a University driver, type IB-60-D, fitted with a long metal extension tube coming from the outside of the room into a shielded, sound proofed room. From the metal tube, the sound was delivered to the ears of the animal in a closed sound system with a 2 mm polyethylene tubing fixed in the canal of the mouse's ear with cement. To obtain beats a second oscillator was used, General Radio oscillator type 1304 B and the two frequencies were mixed electrically to produce the beats. The pure tones and the beats were presented in tone bursts of 100 to 200 msec pulses. The rise time of a tone burst was 7 msec and the decay time 15 msec. The clicks were generated by a Tektronix wave form generator, type 162 and pulse generator, type 161 and were fed into a University driver.

For single unit recordings from the vestibular nerve, tungsten microelectrodes were used with a tip diameter of 1 to 3 microns. The electrodes were coated with Insulex, except at the tip. The indifferent electrode was in the neck muscles. The microelectrodes were connected to a cathode follower and the output amplified with a low level preamplifier, Tektronix type 122 set to a bandpass from 80 cycles per second to 1000 cycles per second. The output of the preamplifier was monitored on a cathode ray oscilloscope, Tektronix type 502 and the responses photographed with a Grass camera. Simultaneously, the output of the preamplifier was passed through a loud

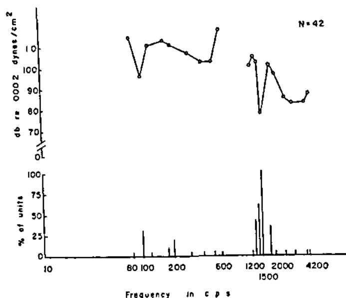


Fig 5 Threshold of vestibular units to sound in the fenestrated Df/Df mice Histogram of units

peaker system for auditory monitoring of unit firing The sound pressure vel delivered to the ear was measured with a Bruel and Kjaer calibrated robe microphone type 4423 and a Bruel and Kjaer wave analyzer, type 107 All readings for the pure tones are re 0 0002 dynes/cm² Click intensities re re human threshold

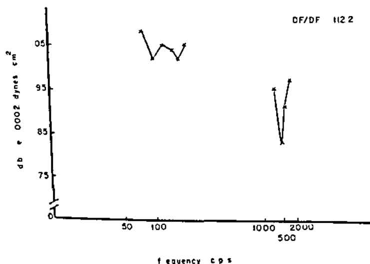
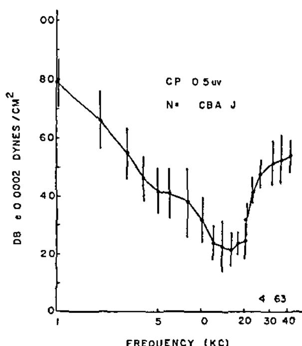


Fig 6 Unit with two separate response areas



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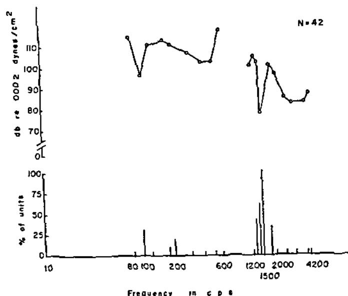


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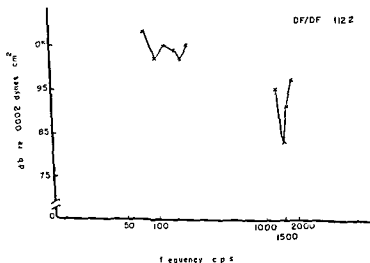


Fig 6 Unit with two separate response areas

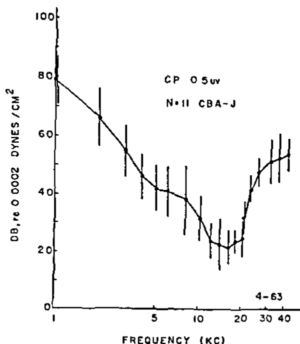


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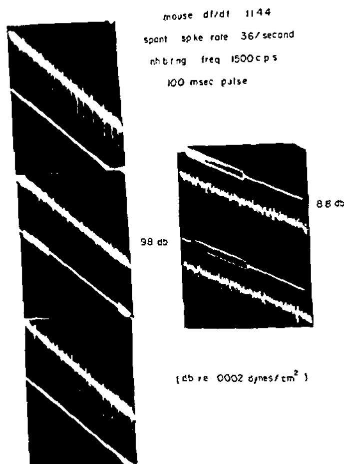


Fig 8 Total and partial inhibition of spontaneous activity in a unit with tone bursts of 1500 c p s Note immediate recovery of activity on discontinuing the tone bursts

per second were tried without any response A threshold curve plotted for the most sensitive units is shown in Fig 5 The most sensitive frequency is at 1500 cycles per second with a threshold of 78 db re 0 0002 dynes/cm² The other frequencies required much more intense tones The histogram of the unit is displayed below the threshold curve of the units in Fig 5 Some units had two response areas (Fig 6) The response pattern of the firing of the single units of the vestibular nerve closely resembled that of a normal auditory unit Firing occurred with a slight delay after the onset of the tone burst (Fig 7) and the number of spikes diminished with a decrease in the intensity of the tone bursts At maximum intensities, some units were inhibi

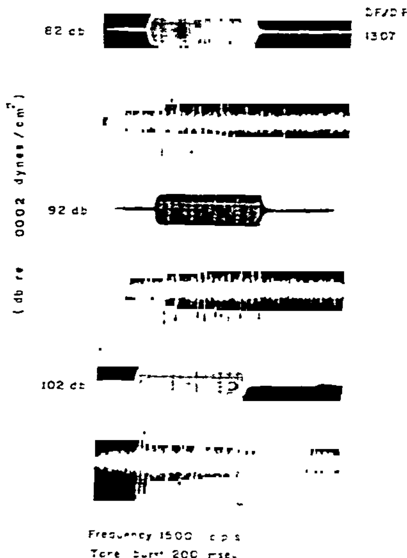


FIG. 7. Response pattern of driven vestibular unit to a tone burst.

RESULTS

1. *Pure tones*

A trial of wide ranges of frequencies showed that the vestibular organ would respond to tones considered to be in the low frequency range for the mouse's cochlea. The single units from the eighth nerve and the cochlear potentials obtained from the normal CBA/J mouse, have a range from 1000 to 40,000 cycles per second with the greatest sensitivity at from 12,000 to 18,000 cycles per second (Fig. 4). The vestibular apparatus in the Df/Df mouse responds best to 1500 cycles per second with a frequency range from 80 to 4200 cycles per second. Frequencies from 80 cycles down to 0.1 cycles

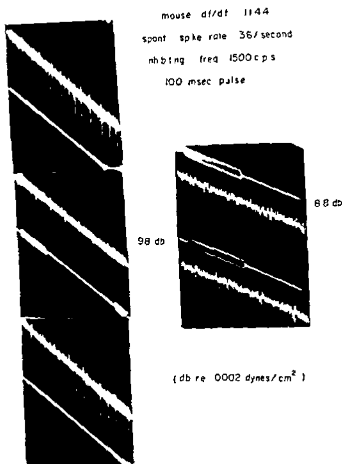


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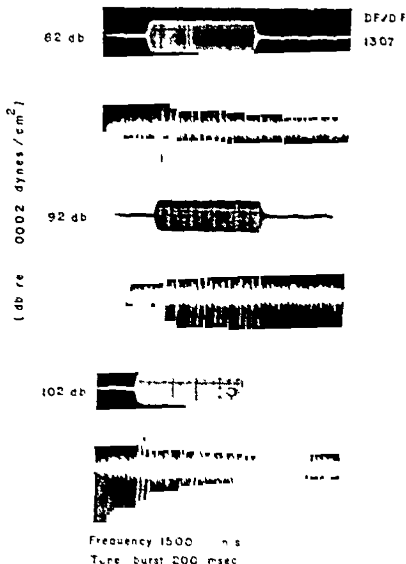


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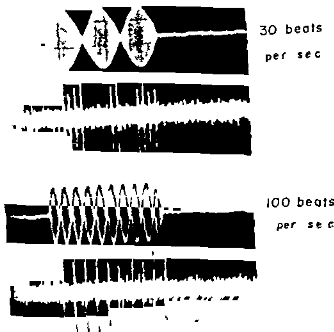


FIG 10 Response pattern of units to beat tones Fundamental frequency of tone is *1500 c p s*

TABLE 1 *Latency and amplitude change of N_1 and N_2 with change in click intensity*

N 12

db[a]	Latency N_1	Amplitude N_1	Amplitude N_2
102	1 17	106	74 4
92	1 20	94	62 8
82	1 34	72	48
72	1 45	52	17

[a] db = re human threshold

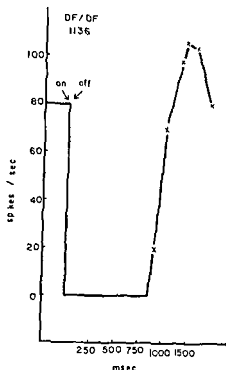


Fig. 9. Inhibition curve of a spontaneous unit. Activity in the unit returns 800 msec after the cessation of the tone burst.

ted partially (Fig. 7). Attempts to obtain driven units to sound in the non-fenestrated Df/Df mice failed. Driven units could be obtained only from the fenestrated mice.

Spontaneous activity was encountered frequently in the vestibular nerve in the fenestrated and non-fenestrated animals, however, only in the fenestrated animals the units were stimulated by tone bursts. In such spontaneous units the after firing was increased and reached the pre-stimulatory level in from 50 to 150 msec. Similarly, spontaneous units were recorded which were inhibited by tone bursts of 1500 cycles per second. Spontaneous activity was inhibited during the tone bursts and activity was resumed immediately after the tone was stopped (Fig. 8). The activity was less suppressed with the reduced intensity of the tone bursts. Other spontaneous units were also inhibited by tone bursts, however, in such units the activity was suppressed immediately with the onset of the tone burst and after a period of no activity in the unit spontaneous spikes would start firing once more and gradually increase and pass the pre-inhibitory level and then diminish to the original levels. Such units required from 500 to 1500 msec to reach the pre-inhibitory activity (Fig. 9).

Bursts of pure tone beats were used and the response pattern observed. The units could follow beats up to a frequency of 140 per second (Fig. 10).

II. *Clicks*

Clicks delivered to the ear elicited a neural response. The click polarity was changed without any change of the polarity of the main event, V_1 and V_2

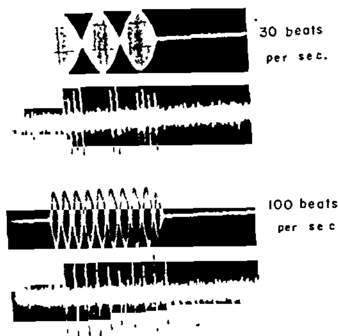


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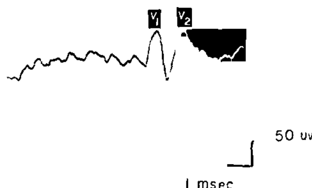


FIG 11 Response to a click 82 db re human threshold Pulse width 0 1 msec

It was observed that clicks of 0 1 msec and wider were required to elicit a response (Fig 11) Such a pulse is considered wide in the normal mouse where click responses are obtained to 0 07 msec pulses and below The latency and amplitude of the responses varied with the click intensities (Table 1) Single unit responses could not be obtained to click stimulation It is

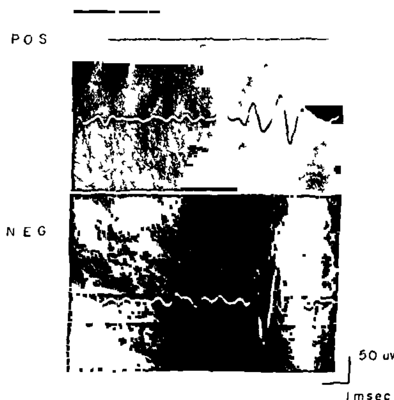


FIG 12 Response to a click with change in polarity 82 db re human threshold

interesting to note that the general configuration of the click response from the vestibular nerve is very similar to an auditory nerve click response and these were labeled V_1 and V_2 denoting vestibular

DISCUSSION

The present experiment demonstrates that the vestibular apparatus in mammals does respond to sound waves To do this it required much more intense tones and also an operative exposure such as fenestration of the semicircular canal It is interesting to note that the response pattern of these units act similarly to other units stimulated by their own specific stimulus for example auditory All of the units responded best to 1500 cycles per second therefore the resonating capacity of the ampulla and the crista or the frequency modulation of the cupula and haircells are more sensitive to these frequencies This type of stimulation differs from the usual type of crista stimulation which is one of deviation to one or the other side such as in caloric and rotation tests The manner the haircells are stimulated in the present experiments is not yet completely established It may be similar to the shearing action (von Békésy 1960) The pattern of spike firing to tone bursts also to beats indicates that the haircells and the cupula are capable of responding to stimuli other than rotation and deviation They also respond to sound waves

As concerns Ewald s second law Dohlman (1963) observed that in muscle recordings an ampullopetal click gave a larger response than the ampullofugal click In the present experiments a negative click which gives an ampullopetal flow results in a larger V_1 and a V_2 from the vestibular nerve than does a positive click which gives an ampullofugal flow (*Fig 12*) however this is again true only for the horizontal canals The intensity of the negative and positive clicks was the same

RÉSUMÉ

Des souris sourds de gendre Dl/Dl ont une dégéneration de la cochlée qui est heréditaire mais ont l appareil vestibulaire normal Dans ces expériments après avoir fait une *fenestration* du canal horizontal on a stimulé l oreile avec des sons pures et des clicks Utilisant la technique de microélectrode on a put obtenir des elements uniques (d *une seule fibre*) du nerf vestibulaire actionnés acoustiquement avec des sons pures et clicks *On a put* obtenir ces elements seulement chez les animaux qui étaient fenestres La bande des fréquences stimulatoire étandait de 80 cycles à 4200 cycles par seconde et la meilleure fréquence était 1500 cycles par seconde avec un seuil d excitation à 78 db re 0 0002 dynes/cm² Les clicks ont donné des réactions grosses On voit ici encore une fois que l appareil vestibulaire réacte aux stimulations acoustiques La manière de stimulation des cellules ciliaires de crête ampullaire n est pas encore absolument claire, mais cela peut ressembler à la Shearing action de Békésy

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THE APPLICATION OF SYNTHETIC GRAFTS IN LARYNGECTOMY AND CLOSING ESOPHAGEAL DEFECTS

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From the Department of Otolaryngology (Head Prof Aleksander Radziminski) Medical Academy Lodz

The author has used knitted polyester nets in plastic surgeries of the esophagus following operations of cancer of the larynx comprising 20 laryngectomies 6 laryngectomies with previous X ray therapy, and 2 cases of closing large esophageal defects after removal of the larynx The operation technique has been discussed and histological investigations have been performed of the nets implanted in the esophagus On the strength of his two years observations the author suggests that knitted polyester nets may be used in plastic surgeries of the esophagus after operations of cancer of the larynx as they prevent the formation of esophageal fistulae after laryngectomy and thus shorten the time of artificial alimentation which makes possible an earlier start of the subsequent X ray therapy The nets can be used successfully in closing large and old esophageal fistulae and defects

Whereas much has been written concerning cancer of the larynx its diagnosis location division different methods of treatment etc less has been said about the postoperative treatment after laryngectomy Very often even a careful operation and tight suturing of the esophagus are followed by the formation of esophageal fistulae the treatment of which is both long and painstaking The fistulae occur especially in those patients who previously to the operation have undergone X ray therapy The penetration of saliva and food through the fistula compel us to feed the patient artificially by means of a feeding tube introduced into the esophagus through the nose These patients will keep asking when the tube is removed so that they can eat normally The prolonged treatment and especially the prolonged artificial alimentation tend to affect the psyche of the patients they become nervous and mentally depressed Moreover sores may result from the prolonged pressure of the feeding tube upon the mucosa of the nose

I have been haunted by the memory of a patient who due to a large esophageal fistula after laryngectomy had to be fed for five weeks through a nasal feeding tube On the day when the tube was finally removed and the patient was allowed to feed normally he became so happy and excited

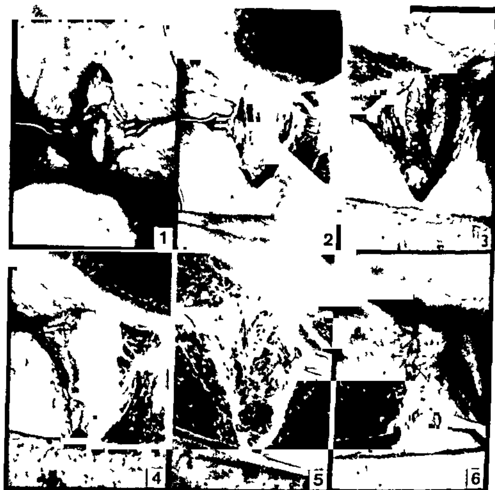


FIG 2 (1) The fistula of the esophagus after laryngectomy, the feeding tube is visible in the background (2) Separation of the mucosa of the esophagus (3) Suturing of the esophagus (4) Knitted polyester net (5) Suturing of the superficial muscles of the neck (6) Complete sewing of the wound

The meshes of the net were filled with granulation, the latter expanding over the surface of the net and forming, after 5–6 weeks, a cicatrice which completely closed the operative wound and healed without further complications

In similar cases, when no net was used, large defects would be recorded The skin growing at the edges of the wound and having no support tends to project into the wound and forms a large fistula Knitted polyester nets produce something in the nature of a scaffold along which expands the granulation which cicatrizes and prevents the formation of a fistula

Encouraged by the good therapeutic results, we applied polyester nets in two cases of plastic surgery of large and old esophageal fistulae Both patients had declined to have laryngectomy and had been prescribed complete X ray therapy A year later they suffered severe dyspnoea and were brought to the clinic where tracheotomy was immediately performed In the patients a large inter-laryngeal tumorous infiltration was found,



Fig 3 The same patient three months after operation

which almost completely closed the lumen of the larynx In either case laryngectomy was performed Unfortunately, because of the post-X-ray changes in the skin and muscles, there occurred necrosis and subsequent breach of the edges of the wound, which gave rise to large esophageal fistulae that defied reclosing Three months later an attempt was made at closing the esophagi with polyester nets Each separated esophagus was carefully closed with a suture and covered with a net which covered the anterior and the lateral sides of the esophagus The next step consisted of dissecting the muscles of the neck far to either side, so that they could be brought close to each other, after which they were tightly sewed together The bleeding during the operation being slight, we were able to close the operative wound completely From then on the patients were nourished through nasal feeding tubes The first dressing after 8 days showed that the wounds had already healed Nonetheless, as we did not want to run the risk of accidental esophageal fistulae or a reopening of the wounds, the feeding tubes were removed not earlier than a fortnight after the operation After the feeding-tubes had been removed, the patients could feed normally and no esophageal fistulae occurred

Figs 2 and 3 illustrate the successive stages of surgical closing of an esophageal fistula

The knitted polyester nets were X-rayed with the full therapeutic dose used in treating cancer of the larynx (Radiological Department, Medical Academy, Lodz—Dr Jakubiszyn), and it has been established that the nets do not absorb the X-rays Experimental investigations of the behaviour of knitted polyester nets in living organisms have been conducted, with rabbits, by Kuś, Szendzikowski and Szenic, and, in man, by Jasiński, Mioduszewska & Szendzikowski (1963) The latter investigators had selected a net measuring 1 × 3 cm and implanted it between the intercostal muscles and the surrounding fascia in men who were to be operated on the chest.

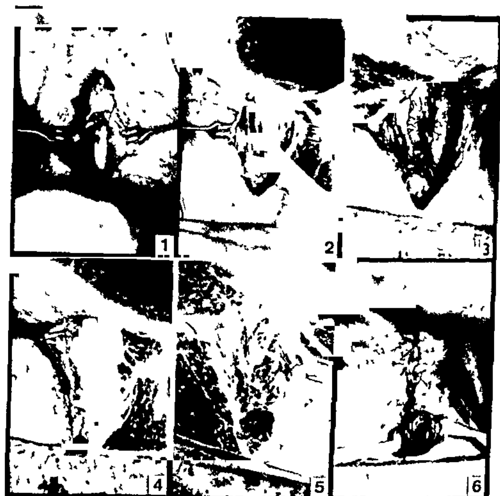


Fig. 2. (1) The fistula of the esophagus after laryngectomy; the feeding tube is visible in the background. (2) Separation of the mucosa of the esophagus. (3) Suturing of the esophagus. (4) Knitted polyester net. (5) Suturing of the superficial muscles of the neck. (6) Complete sewing of the wound.

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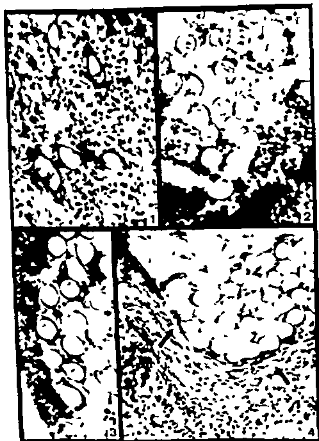


Fig 5 Micr photograph performed in the Department of Pathological Anatomy Medical Academy Lódz Preparations were stained with hematoxylin and eosin (1) Granulation magnified 250 times (2) and (3) Fibres of the net—peripheral hematic infusions Some fibres are adhered to by flattened mononuclear cells Magnified 55 times (4) Yarns of the net—the early formation of a young connective tissue stroma m rked with arrows Magnified 450 times

On the twentieth day a sample of the net with the surrounding tissues was taken out for histological examination (preparations Histological Department Medical Academy Lodz—director Prof T Pawlikowski) The result of the histological examination reported by Szendzikowski (Department of Pathological Anatomy Medical Academy Lodz—director Prof A Pruszczynski) was the following

Microscopically (Fig 1) there was visible a profusely vascularized granulation with scattered all resorptive leucocytes Cross-sections of polyester yarns were also visible Round some of the yarns there were signs of an early organisation consisting of flattened mononuclear cells (Figs 2 and 3) which adhered to the yarns of the prosthesis Other yarns were directly surrounded by granulation (Fig 4) which formed a stroma of

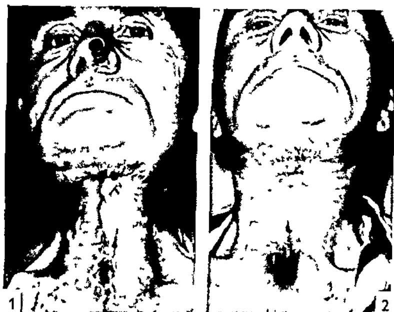


Fig. 4. (1) The patient with necrosis of the skin and muscles after laryngectomy, the implanted polyester net is visible in the background. (2) The same patient with the wound healed.

The net with the surrounding tissue was removed on the 3rd, 4th, 5th, 7th, 14th, 30th and 52th days, respectively, and was subjected to comparative histopathological examinations. As the result of their observations, Jasiński, Mioduszewska & Szendzikowski (1963) arrived at the conclusion that, in man, the tissue reaction to the net during the 3–52 days following the implantation did not exceed the limit of reaction to a chemically indifferent foreign body.

On our part we have also been able to carry out histological investigations on a patient with cancer of the larynx, who came to our clinic after a complete X-ray therapy. The cancer was large and covered the ingress to the larynx and the whole epiglottis, and was infiltrating into the base of the tongue, the skin in the region of the infiltration and the lymphatic glands. The esophagus was covered with a knitted polyester net as described above. After 10 days there occurred necrosis of the skin and muscles, and the wound reopened. Deep down in the wound there was visible the net, peripherally coalescing with the deeper layers of the muscles. Granulation was spreading from the edges and over the net, forming a cicatrice that completely closed the operative wound. Only in the region corresponding to the base of the tongue, i.e. in the upper part of the net, there was a small fistula which was closed after reshaping the edges, and the patient was able to feed normally.

It is known from experience that in similar cases, especially when there is a tumorous infiltration into the skin, there occur defects of the skin, muscles and esophagus that require prolonged treatment and repeated plastic surgeries.

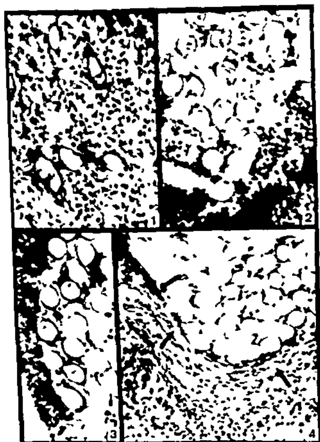


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young connective tissue The granulation round the yarns of the net showed no clear tissue reaction, as it was devoid of polynuclear giant cells

Upon repeated verifying examinations it became manifest that knitted polyester nets provoke no subsequent inflammatory reaction. Only in three cases small superficial fistulae *appeared in the course of 3–4 months after* the operations, secreting a small amount of hemomucous exudate A bacteriological examination proved the exudate to be sterile It ought to be noted that the fistulae were unconnected with the esophagus, as no aliment, including liquids penetrated through them, although the patients had been feeding normally In one of the cases the fistula healed in a few days when a drain with oxycort had been introduced In one of the remaining two cases it was necessary to remove part of the net, and the fistula persisted throughout a long time The net was removed without much difficulty Here, *although the implantation of the net was not successful, it never*theless had served its purpose, for during the process of healing of the esophagus it supported the latter's sides and prevented the formation of an esophageal fistula On the basis of our observations made during two years we suggest that knitted polyester nets may be successfully applied in plastic surgery of the esophagus after cancer of the larynx, as they provide

1 Prevention of the formation of esophageal fistulae and thereby, a *shortening of the time of the postoperative treatment*
2 Reduction of the *period of artificial alimentation*
3 An earlier start for subsequent X-ray therapy, which in many cases is a decisive factor for good therapeutic results
4 The possibility of closing large and old esophageal fistulae and defects after laryngectomy, even with previous X-ray therapy It eliminates the necessity of additional operations such as transplantations of skin from other parts of the body

RÉSUMÉ

L'auteur a appliqué un filet de polyestre pour la plastique de l'œsophage dans 20 cas de laryngectomie 6 cas de laryngectomie après la radiothérapie et 2 cas de larges déficits de l'œsophage après l'enlèvement du larynx Il a discuté la *technique opératoire Les examens histopathologiques du filet polyestre trans*planté à l'œsophage ont été effectués

En vertu des observations de deux ans l'auteur croit que le filet polyestre peut être appliqué pour la plastique de l'œsophage Dans cette méthode on préserve la *formation des fistules après la laryngectomie ce qui raccourcit le temps de l'alimentation artificielle et rends* possible la radiothérapie plus tôt On peut appliquer le filet polyestre avec les résultats satisfaisants pour la fermeture des larges fistules et anciens déficits de l'œsophage après les opérations du larynx

ZUSAMMENFASSUNG

Der Autor wandte ein *polyesteriertes Netz zur* Ösophagusplastik nach Kehlkopfkrebsoperationen an, und zwar in 20 Laryngektomien, 6 Laryngektomien

nach vorheriger Röntgenbestrahlung und 2 Fällen grosser Ösophagusdefekte nach Resektion des Kehlkopfes Die Technik des chirurgischen Eingriffs wird besprochen Histopathologische Untersuchungen des im Ösophagus implantierten polyesterierten Netzes wurden ausgeführt

Auf Grund seiner zweijährigen Beobachtungen ist der Autor der Ansicht, dass das polyesterierte Netz für Plastik des Ösophagus nach Kehlkopfoperationen angewendet werden kann weil es Schutz gegen Ösophagusfistelbildung nach erfolgter Laryngektomie bietet und somit auch die Zeitperiode künstlicher Ernährung verkürzt was eine schnellere Röntgennachbestrahlung ermöglicht Das polyesterierte Netz kann ebenfalls mit gutem Erfolg zur Überdeckung grosser alter Fisteln und Ösophagusdefekte nach Kehlkopfoperationen angewendet werden

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4. The possibility of closing large and old esophageal fistulae and defects after laryngectomy, even with previous X-ray therapy. It eliminates the necessity of additional operations such as transplantations of skin from other parts of the body.

RÉSUMÉ

L'auteur a applique un filet de polyestre pour la plastique de l'œsophage dans 20 cas de laryngectomie, 6 cas de laryngectomie apres la radiotherapie et 2 cas de larges deficits de l'œsophage apres l'enlevement du larynx. Il a discute la *technique operatoire*. Les examens histopathologiques du filet polyestre transplante a l'œsophage ont ete effectues.

En vertu des observations de deux ans l'auteur croit que le filet polyèstre peut etre applique pour la plastique de l'œsophage. *Dans cette methode on preserve* la formation des fistules apres la laryngectomie, ce qui raccourcit le temps de l'alimentation artificielle et rends possible la radiotherapie plus tot. On peut appliquer le filet polyestre avec les resultats satisfaisants pour la fermeture des larges fistules et anciens deficits de l'œsophage apres les operations du larynx.

ZUSAMMENFASSUNG

Der Autor wandte ein polyestergewirktes Netz zur Ösophagusplastik nach Kehlkopfkrebsoperationen an, und zwar in 20 *Laryngektomien*, 6 Laryngektomien

another serum sample was obtained during the convalescent phase. Faecal specimens from 38 of the children were virologically examined. The treatment of the children with pseudocroup was performed according to the following principles. All patients received an expectorant and an antihistaminic preparation (Promethazine). Patients with fever were treated with antibiotics of the broad spectrum type (Chloramphenicol or Oxacillin). Those patients who at admission had pronounced respiratory difficulties were immediately given one intramuscular injection of a steroid (Dexamethason 21 phosphate 4 mg) which was repeated if the respiratory difficulties persisted.

Of the 181 cases with pseudocroup 51 were examined with isolation attempts from throat swabs as well as complement fixation (CF) tests of sera from the acute and convalescent phases. From another 45 cases throat swabs were virologically examined but from these patients no convalescent phase sera were received.

The children were discharged from the hospital when all symptoms had subsided and they were afebrile. Virologically examined patients were asked to return in about 2 weeks after discharge and second serum samples were then taken.

Control material. Throat and nose swabs from children treated at the children's hospital of Gothenburg which were sent for routine virologic examination, were used as a control material. Forty three such specimens from 36 children without pseudocroup but with suspect viral disease were obtained during the investigation period.

Thirty two serum samples from children in the same age group as the pseudocroup children sent to the virological laboratory for routine tests during the investigation period were employed as control serum specimens. Most of the children in this series had mental diseases, congenital malformations or eye diseases. For 9 of these signs of respiratory illness had been recorded.

Isolation of agents. Each faecal or throat specimen was added to two monkey kidney cell cultures and two cultures of HeLa cells or trypsinized human embryonic kidney. The cells were maintained in Hanks' balanced salt solution with 0.5 per cent lactalbumin hydrolysate and 7 per cent calf serum. The cultures were read every day. The maintenance medium was changed every 3rd day. After 6 days the fluid in the cultures was tested for chicken erythrocyte agglutinating activity and at the same time hemadsorption tests with guinea pig erythrocytes as described by Vogel & Shelokov (1957) were performed. A blind passage was always made and after another 6 days haemagglutination and haemadsorption tests were repeated.

Typing of agents. Cytopathogenic agents were typed with the aid of specific hyperimmune sera in tissue cultures. Haemadsorbing (HA) agents were typed in complement fixation tests. The agents were passed to monkey kidney

PSEUDOCROUP ASSOCIATED WITH VIRAL INFECTIONS

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During 1963 (January through April) 96 children with pseudocroup in Gothenburg were virologically investigated by means of isolation attempts from throat swabs and faecal specimens. Paired sera obtained from 51 cases were tested for complement fixing antibodies against parainfluenza, influenza and adeno virus antigens. Evidence for infection with parainfluenza 1 virus was obtained in 18 cases, parainfluenza 2 in 2, influenza A in 5 and adenovirus in 2 cases. In most clinical respects the cases with evidence of the different viral infections were similar to those with unknown etiology.

Pseudocroup or subglottic laryngitis is a disease with an etiology which has not as yet been fully established. Bacteria of different types have been proposed as causative agents. Rabe (1948) and Philipson (1958) however found that bacterial infection was not an important factor in their material of pseudocroup cases. Allergic factors may be involved in the pathogenesis of pseudocroup (Horesh 1951, Philipson 1958).

The viral etiology of pseudocroup has gained much interest during the last years and accumulating evidence has been presented indicating that viral infections are associated with a majority of pseudocroup cases. In particular viruses of the myxovirus group have been condemned as causative agents. Recent investigations have shown that parainfluenza viruses are often associated with pseudocroup. In addition influenza, adenovirus and ECHO viruses seem to be possible causative agents.

The aim of the present investigation was to determine the role played by parainfluenza, influenza and adenovirus for the pathogenesis of pseudocroup in patients in Gothenburg, Sweden.

MATERIAL AND METHODS

In 1963, from January through April, 171 patients with pseudocroup were admitted to the ENT department at the Sahlgrenska hospital, Gothenburg. Since the condition recurred in some of the children the total number of admissions was 181 during the investigation period. From a total of 96 children swabs of the rhinopharynx and acute phase blood samples were obtained within the first hours after admission. From 53 of these cases

another serum sample was obtained during the convalescent phase Faecal specimens from 38 of the children were virologically examined The treatment of the children with pseudocroup was performed according to the following principles All patients received an expectorant and an antihistaminic preparation (Promethazine) Patients with fever were treated with antibiotics of the broad spectrum type (Chloramphenicol or Oxacillin) Those patients, who at admission had pronounced respiratory difficulties were immediately given one intramuscular injection of a steroid (Dexamethason 21 phosphate 4 mg) which was repeated if the respiratory difficulties persisted

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Isolation of agents Each faecal or throat specimen was added to two monkey kidney cell cultures and two cultures of HeLa cells or trypsinized human embryonic kidney The cells were maintained in Hanks balanced salt solution with 0 5 per cent lactalbumin hydrolysate and 7 per cent calf serum The cultures were read every day The maintenance medium was changed every 3rd day After 6 days the fluid in the cultures was tested for chicken erythrocyte agglutinating activity and at the same time hemadsorption tests with guinea pig erythrocytes as described by Vogel & Shelokov (1957) were performed A blind passage was always made and after another 6 days haemagglutination and haemadsorption tests were repeated

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Complement fixation test (CF test). The test was performed in a micromodification on plexiglass plates described by Fulton & Dumbell (1949). The sera were tested in dilutions ranging from 1/4 or 1/8 to 1/256 against antigens derived from parainfluenza 1, 2 and 3, influenza A and B and adenovirus. Antigen and serum controls as well as complement titration were included in all tests.

RESULTS

Virologic Findings

Altogether 4 cytopathogenic and 20 HA agents were isolated in tissue culture. The HA agents were all positive in both haemadsorption and haemagglutination tests. All but one of the agents were recovered from throat swabs. Of the cytopathogenic agents isolated, 2 gave a cytopathogenic effect on HeLa cells resembling that of respiratory syncytial (RS) virus. The other 2 cytopathogenic agents were identified as adenovirus (isolated from faeces) and coxsackie B 4 virus.

Paired sera were available from the case with recovery of adenovirus and one case with recovery of RS resembling virus. No neutralizing antibodies against the corresponding viruses could be shown in any of these sera at a lowest dilution of 1:10.

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Paired sera which were obtained in all these cases were tested for complement fixing antibodies. A four fold rise in antibody titer was considered significant evidence of infection.

	4-fold or greater rise in CF antibody titer		2-fold rise in CF antibody titer or titers ...		Titers against all antigens ...	
	HA agent recovered	*HA agent* not recovered	*HA agent* recovered	*HA agent* not recovered	*HA agent* recovered	*HA agent* not recovered
Parainfluenza 1	5	1	[a]			
2	0			1[a]		
3	[illegible]		[illegible]	1		
Influenza A	[illegible]		1	3[a]		
Influenza B	[illegible]					
Adeno				1		
Total		1	3	8	[illegible]	[illegible]

[a] T... patients ... significant ... evidence of ... concurrent infection with two viruses ... in one case with influenza A ... parainfluenza 1 ... in the other with influenza A and ... parainfluenza ...

[illegible]

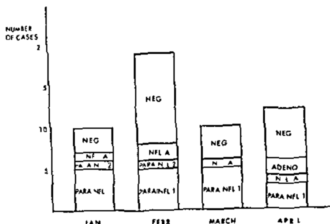


Fig 1 Monthly distribution of serologic findings in 51 pseudocroup cases As positive cases are regarded only those with significant titer increase

All of the 20 HA agents were isolated on monkey kidney cells Six of these agents which after repeated passages occurred in such concentrations that it was possible to type them in the CF test, were identified as parainfluenza 1 virus

The results found in cases with both serologic and virologic investigations performed are shown in Table 1 Significant fourfold increase in CF antibodies from acute to convalescent phase sera was noted for parainfluenza 1 in 18 cases parainfluenza 2 in 2 influenza A in 5 and adenovirus in 2 cases Serologic results indicating simultaneous infection with two viruses were obtained in two cases

In the fully examined group HA agents were isolated in 13 cases and 4 of these agents were identified as parainfluenza 1 virus Recovery of HA agents without corresponding positive findings in the serologic tests was obtained in 3 cases

Fig 1 shows the monthly distribution of the serologic findings In this figure only the cases with significant titer increase are considered positive

TABLE 2 *Complement fixation test titers in 32 sera from children without pseudocroup*

Sera were obtained during the investigation period from children 1 to 5 years old with different diagnoses including upper respiratory infections

	<8	8	16	≥32
Adeno	31	1	0	0
Parainfluenza 1	25	4	2	1
2	32	0	0	0
3	32	0	0	0
Influenza A	29	2	1	0
Influenza B	32	0	0	0

cell cultures with Hanks' solution and lactalbumin hydrolysate but without calf serum. After some days the culture fluids were pipetted off and tested against parainfluenza and influenza specific antisera in complement fixation tests.

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	HA agent recovered	HA agent not recovered	HA agent recovered	HA agent not recovered	HA agent recovered	HA agent not recovered
Parainfluenza 1	8	10	2[a]	2		
2	0		0	1[a]		
3	0	0	0	1		
Influenza A	0	[illegible]	1[a]	3[a]		
Influenza B	0	0	0	0		
Adeno	0		0	1		
Total	8	[illegible]	3	8	3	12

[a] Two patients had [illegible] of concurrent infection with two viruses, in one case with influenza A [illegible] in the other with influenza A and parainfluenza 2.

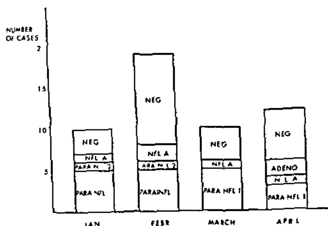


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	4 fold or greater rise in CF antibody titer		2 fold rise in CF antibody titer or titers ≥ 16		Titers against all antigens < 16	
	HA agent recovered	HA agent not recovered	HA agent recovered	HA agent not recovered	HA agent recovered	HA agent not recovered
Parainfluenza 1	[illegible]	1	[illegible][a]			
2	0		[illegible]	1[a]		
3	0		0	1		
Influenza A	[illegible]		1[a]	[illegible][a]		
Influenza B				[illegible]		
Adeno	0		[illegible]	1		
Total	[illegible]	1		8	1	[illegible]

[a] Two patients had concomitant [illegible] of concurrent infection with two viruses, in one case with influenza A and [illegible], in the other with influenza A and parainfluenza 2.

Different kinds of infectious complications, such as otitis, bronchitis or cervical adenopathy, occurred in some cases. There was, however, no predominance of complications in any of the virologically positive groups. Of 4 roentgenologically verified cases of bronchopneumonia in the virologically examined material, one was a patient with parainfluenza infection, one a patient with suspect RSV infection, one a patient with suspect adenovirus infection and one a virologically negative case.

The majority of the pseudocroup cases were considered to be mild or moderate and only 29 of 181 had severe respiratory difficulties. Two boys, 3 and 8 years old, required tracheotomy. The severity of the pseudocroup was not found to be more pronounced in any one of the virologically positive groups.

The temperature was found to be elevated in the majority of the patients with pseudocroup. A tendency toward higher temperature levels was found in the parainfluenza and influenza groups.

Of the 181 cases 82 were considered to have symptoms of such a severity that steroids were administered at admission. Of the 27 cases with significant increase in antibodies 12 had been given steroids. Fifteen out of 24 patients who did not develop a significant antibody response had been treated with steroids.

DISCUSSION

The investigation period was chosen to coincide with a period of time when many pseudocroup cases could be expected, that is during the first 4 months of the year. In 1963 a total of 283 cases were treated in the ENT department; thus the 181 cases in the present material comprises almost 2/3 of the year's cases.

The serologic results in the present report showed an association of parainfluenza 1 in 18, parainfluenza 2 in 2, influenza A in 5 and adenovirus in 2 cases out of the 51 serologically examined cases. Inconclusive but suggestive results indicating viral infection were obtained in another 12 cases. Thus in 54 % a certain and in an additional 23.5 % a probable association of viral infection with pseudocroup illness was obtained.

The isolation attempts from the control material gave positive results only when specimens were taken from patients suffering from acute respiratory disease. This finding indicates that the demonstration of HA agents in the pseudocroup cases can probably be associated with the current illness.

The finding of the predominant association of parainfluenza 1 infection is consistent with the results of Vargosko *et al.* (1958), McLean *et al.* (1962), Blyumental & Bukrinskaya (1962) and van der Veen & Smeur (1961). The Russian investigators found almost as many influenza as parainfluenza 1 cases in their material. Parrot *et al.* (1962) found that 27 % of the children hospitalized with influenza A2 or B infection had pseudocroup. In the present investigation only 5 out of 51 cases were diagnosed as influenza A, in spite of the fact that influenza A2 was epidemic in Gothenburg during the investiga-

Parainfluenza and influenza A infections were diagnosed during the whole period.

Control material. Rhinopharynx specimens from the 36 control children were in 4 cases found to contain HA agents. Two of these patients had acute bronchitis and the other two had acute laryngitis. No cytopathogenic agents were isolated from this material. The 32 control sera were examined for CF antibodies against parainfluenza, influenza and adeno antigens. Antibodies in low titers could be demonstrated against parainfluenza 1 more frequently than antibodies against the other types of antigens. The results of the serologic investigations of the 32 sera are given in Table 2.

Clinical Findings

In Table 3 the results of the clinical investigation of the total material are compared with the findings in the virologically positive cases. From the table it can be seen that boys were twice as common as girls in the total material as well as in the positive cases. The mean age in the total material was 46 months. The mean age of the virologically positive cases did not show any great difference from the total material. The uncomplicated pseudocroup cases were usually discharged within 5 days. Some patients with longterm fever or infectious complications were hospitalized more than 5 days. The average number of days of hospitalization was 3.3. In the parainfluenza group this figure was 3.8 days.

TABLE 3. *Clinical findings in total material and in serologically positive cases*

	Sex ♂ ♀	Mean age (months)	Days at hospital	Severity of pseudocroup[a]	Max. temp.[b]
Total material	119 6[illegible]	46	3.3	A 29 B 51 C 100	A 51 B 98 C [illegible]8
Parainfluenza	14 6	48	3.9	A 3 B 6 C 11	A [illegible] B 13 C 2
Influenza	5 0	62	3.0	A 0 B 3 C 2	A [illegible] B 3 C [illegible]
Adenovirus	2 0	57	5	A 0 B 0 C 2	A 1 B 0 C 1

[a] Number of cases with (A) Typical cough, stridulous breathing and indrawings of the chest wall; (B) Typical cough, slightly stridulous breathing; (C) Typical cough, slightly stridulous breathing only with anxiety.

[b] Number of cases with temperature (A) More than 3[illegible]; (B) 37.5–38.[illegible]; (C) Less than 37.[illegible]

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tion period. Influenza B infections which have been associated with pseudocroup by McLean *et al.* (1962) were occasionally diagnosed in Gothenburg during the period in question, although in none of the pseudocroup cases.

The findings in the control material indicated that parainfluenza 1 was more prevalent than the other studied viruses but occurred at a much lower frequency than in the pseudocroup material during the investigation period. The control material, however, was too small to permit definitive conclusions on parainfluenza 1 as a causative agent of pseudocroup relative to its potency as cause of other respiratory infections.

Evidence of infection with ECHO 11 which was predominant in the investigation of Philipson (1958) was not obtained in the Gothenburg area during the investigation period. Chanock (1956) and Beale *et al.* (1958) found parainfluenza 2 virus to be associated with 45 to 66 per cent of the pseudocroup cases studied. This virus has in more recent investigations, including the present one, been related to a certain number of pseudocroup cases but not to the extent found by Beale and Chanock. Kapikian *et al.* (1963) found that out of 20 children with respiratory illness of parainfluenza 2 origin only one developed pseudocroup.

As the results have shown the present material can be regarded as representative from a clinical viewpoint. In most respects such as age and sex distribution, time of hospitalization and degree of severity of the pseudocroup the different groups with established viral etiology are similar to the total material. The 5 pseudocroup cases serologically diagnosed as influenza had mild pseudocroup symptoms but on the other hand a tendency toward high fever. The relative mildness of the disease in these cases is not in agreement with some other materials where the pseudocroup often progressed to an obstructive membraneous laryngotracheobronchitis with high fever, severe respiratory difficulties and high mortality (Forbes, 1958, Bauer, 1959).

It seems to be difficult to correlate the severity of clinical symptoms in a given case of pseudocroup to any particular viral etiology. There was no predominance of mild infectious complications or bronchopneumonia in any of the groups with viral origin.

Patients with pseudocroup are generally treated with antibiotics if they are febrile at admission to hospital. As there is now an accumulation of evidence pointing toward viral etiology in a high percentage of pseudocroup cases this treatment must be surveyed with renewed scepticism. An argument in favor of antibiotic therapy is the risk for secondary bacterial invasion after viral infection.

Another problem in the treatment of pseudocroup is the possibility that administration of corticosteroids can impair the antibody response and thus increase the risk for a quick recurrence of the disease. In the present material the corticosteroids were as a rule given only as a single intramuscular injection at admission to hospital. It seems unlikely that the dosage used should have any great influence on the antibody response. In the total material as

in the cases with established viral association slightly less than half of the patients received steroid treatment. In the group where no titer increase could be demonstrated, however, it was more common that the patients had been treated with steroids.

The viral etiology of pseudocroup seems to be heterogenic and may be changing from time to time. On the other hand parainfluenza 1 virus seems to be the agent most commonly associated with pseudocroup illness. This assumption raises the question whether or not immunoprophylaxis might be of aid for the prevention of pseudocroup. Hamparian *et al.* (1961) found that a killed bovine parainfluenza 3 vaccine in a mineral oil emulsified vaccine was highly efficacious in producing immunity in the vaccinated animals. It seems probable that effective parainfluenza vaccines also against infections in humans can be prepared.

The frequency of parainfluenza 1 infection in children with recurrent pseudocroup has not been determined in the present investigation. Chanock *et al.* (1961) have suggested, however, that parainfluenza viruses can probably infect the same person two or more times and that the natural infection thus does not necessarily produce immunity. Immunization by vaccination against parainfluenza might therefore possibly also be useful for the prevention of recurrent pseudocroup.

ACKNOWLEDGEMENT

The skillful technical assistance of Miss Mona Eriksson and Miss Margreth Petterson is gratefully acknowledged.

ZUSAMMENFASSUNG

Während des Jahres 1963 (Januar bis April) wurden in Gotenburg an Rachen- und Facesproben von 96 Kindern mit Pseudocroup virologische Isolierungsversuche unternommen. Doppelproben von 51 Seren wurden auf komplementbindende Antikörper gegen Parainfluenza-, Influenza- und Adenoantigene untersucht. Infektion mit Parainfluenza 1 wurde in 18 Fällen nachgewiesen, Parainfluenza 2 in 2, Influenza A in 5 und Adeno in 2 Fällen. Die virologisch positiven Fälle wiesen in klinischer Hinsicht kaum Unterschiede zu denen mit unaufgeklärter Ätiologie auf.

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REPEATED VERTICAL SEMICIRCULAR CANAL STIMULATION DOES NOT HABITUATE HORIZONTAL NYSTAGMUS IN CAT

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From the U S Army Medical Research Laboratory Fort Knox

A group of cats was exposed to a series of angular accelerations about a vertical rotatory axis with the head tilted so that a synergic pair of vertical canals were in the plane of rotation and then tested with the lateral canals in the plane of rotation This group was compared with a second group that received only lateral canal stimulation and with a third group that received neither lateral nor vertical canal stimulation It was found that repeated acceleration of the vertical canals does not reduce that nystagmus elicited with the lateral canals accelerated in the plane of rotation

The reduction in nystagmic output which occurs with repeated elicitation is termed habituation There is increasing evidence that nystagmus habituation is not simply a general loss of reflex excitability but that it is a reduction specifically related to well defined and circumscribed aspects of the repeated stimulus This decline is found in the cat even when severe alerting or arousal measures are taken (Crampton 1964 Crampton & Schwam 1961) is specific to the direction of angular acceleration (Collins 1964 Crampton 1962 *a*) and is not influenced by at least three varieties of visual experience during rotation (Crampton 1962 *b*) It remains to be determined if nystagmus habituation is specific to the plane of rotatory stimulation For example, will many angular accelerations in the plane of a pair of vertical canals produce a habituation of nystagmus elicited when the lateral canals are in the plane of rotation?

Three groups of twenty cats each were employed in this experiment Each animal received ten acceleration trials The 1st and 10th trials were identical for all three groups in that the cats were fixed with the lateral canals in approximately the horizontal plane the plane of turntable rotation For the intermediate trials 2 through 9 cats from one group were tilted so that a pair of vertical canals were in the horizontal plane A second group of cats received all 10 trials in the horizontal position and a third group received no accelerations but was tilted and maintained at constant velocity Eye movements were electrically recorded the cats were maintained in a high state of arousal with d amphetamine sulfate testing was

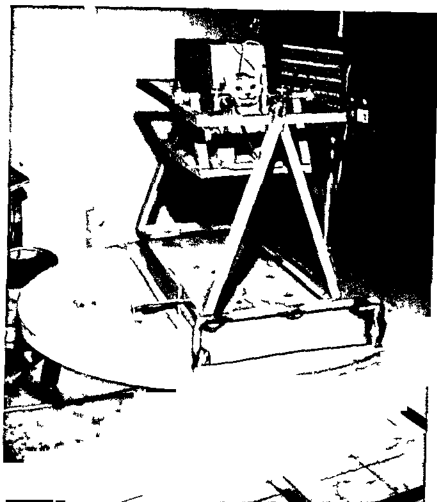


FIG 1 Cat restrained and positioned with the lateral canals approximately in the horizontal plane of rotation The head is aligned with both the vertical axis of rotation and the horizontal axes of the gimbals which support the restraining box

in total darkness and light and dark adaptation were controlled Specificity of habituation to the plane of rotation was evaluated by comparison of the nystagmic responses of the three groups to trial 10

METHODS

Stimulator and recording system

The circular horizontal turntable 1 25 meters in diameter is driven about a vertical axis by means of a friction rim drive coupled to an electro hydraulic motor control system Constant angular accelerations of precise duration and magnitude are programmed from a console outside the radio frequency shielded light proof and ventilated room which houses the turntable itself Electro nystagmogram signals picked up by needle electrodes inserted at the outer canthi lead through slip rings to an ink writing recorder at the outside control console Eye movements are recorded with balanced amplifier inputs and a 1 7 sec RC coupling time constant

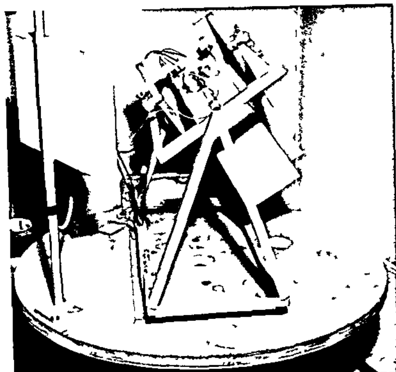


Fig. 2 Cat restrained and positioned with the superior vertical canal of the left side and the posterior vertical canal of the right side in the plane of turntable rotation The head is still aligned over the axis of rotation in this tilted position

Procedure

Mature cats that had not been accelerated previously were employed At least two days prior to testing each animal was anesthetized and small holes were drilled through the canine teeth On the day of testing and 60 to 90 minutes prior to the 1st trial the animal received a 2 5 mg/kg interperitoneal injection of *d* amphetamine sulfate Each cat was then restrained in a special box and piano wire strung through the teeth and drawn taut according to the efficient and humane restraint technique devised by Henriksson Fernandez & Kohut (1961) The box was then positioned on the turntable as shown in Fig 1 Needle electrodes were inserted in folds of skin at the outer canthi and a ground wire attached to the piano wire strung through the teeth The turntable was accelerated with a subthreshold value to 6 0 rpm and the room lights turned on The amplifier was then adjusted to an optimal gain for the optokinetic nystagmus the lights turned off and the animal returned with a subthreshold acceleration to zero rpm After ten minutes in total darkness the first trial was begun

All trials consisted of an 8 0°/sec² positive acceleration of 15 0 sec duration which brought the turntable from a stop to 20 0 rpm clockwise rotation After 30 sec of constant velocity at 20 0 rpm the table was returned

to a stop with a negative, but subthreshold acceleration lasting 9.5 minutes.

Following the 1st trial, the lights were turned on for five minutes, during which time animals in groups *A* and *B* were positioned as shown in Fig. 2, and group *C* animals were left in the horizontal position. Ten minutes of dark adaptation then ensued for animals of all three groups. Animals in group *B* were accelerated at a subthreshold rate to 10.0 rpm and held at that angular velocity for one hour and ten minutes. Following the first ten minutes of dark adaptation, animals in groups *A* and *C* were subjected to trials 2 through 9.

Prior to the 10th trial, group *B* animals were returned to a stop with a subthreshold acceleration. The lights were turned on for five minutes for all groups, and cats in groups *A* and *B* were returned to the horizontal position shown in Fig. 1. All groups were given 10 minutes of dark adaptation and trial 10 was then begun.

Eye movements were recorded for all groups on trials 1 and 10, and on the intervening trials for group *C*. Eye movement recording was started just prior to the onset of the acceleration and continued throughout the period of primary nystagmus and until the secondary nystagmus was well developed.

Calibration

Following the 10th and final trial, animals were brought to 6.0 rpm, light adaptated for 5.0 minutes and a 30 sec sample of optokinetic eye movements recorded. The slow-phase slope thus recorded at the 36°/sec velocity of the visual field provided the calibration standard.

RESULTS

The primary nystagmus for trials 1 and 10 for groups *A* and *B* and for all 10 trials for group *C* was hand measured. The vertical displacement of each slow-phase movement was measured in millimeters and summed for each second of recording (Fig. 3). With a recording paper speed of 25 mm/sec and θ representing the slow-phase angle of optokinetic nystagmus recorded with a 36°/sec velocity of the visual field, the degrees of slow-phase vestibular nystagmus is approximated by

$$\text{Degrees of slow-phase} = (1.44 \text{ cotangent } \theta) \text{ mm of slow-phase}$$

For this experiment, the total number of degrees slow-phase movement for each entire period of primary nystagmus was summed to give what is hereafter referred to as an "output score".

The variance of nystagmus output scores is greater about high output means than about low output means, a circumstance that may lead to statistical difficulties. Homogeneity of variance was gained by using the logarithms of each output score for analysis. The means shown in Fig. 4

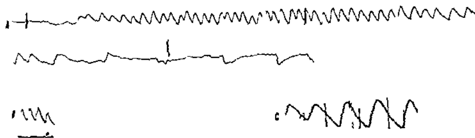


FIG 3 The upper two lines show a response of a cat to an 8.0°/sec² positive acceleration *of 15 sec duration The period of acceleration is between the heavy short vertical lines* The primary nystagmus with fast phase to the right is shown with fast phase up Onset of the secondary nystagmus, typically more prominent in cat than in man is shown by the arrow The secondary nystagmus continued for some 15 sec longer than is shown here In the lower left is a brief sample of the optokinetic response *recorded at a 36°/sec rotation of the visual field The geometric construction* shows the determination of the slope angle Θ In the lower right an enlarged segment of vestibular nystagmus is marked into two 1 sec *intervals with dotted lines and the vertical displacement of the* slow phase activity is indicated with solid lines

are geometric means and the standard errors of the means were computed with the logarithmic transformation Figure 4 shows that only group *C* *displayed a marked habituation of nystagmic output, and* groups A and *B* declined little if at all

Analysis of covariance was used to evaluate the data from trials 1 and 10 This statistical analysis (Edwards 1950) takes into account the differences due to sampling between groups on trial 1 in the evaluation of differences between groups on trial 10 The summary of this analysis is shown in Table 1 Considering all three groups there are significant differences on trial 10 When each pair combination is considered group *C* differs

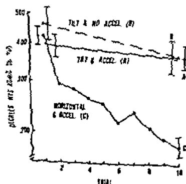


FIG 4 Geometric means of the nystagmic output per trial for the three groups Standard errors of the means are indicated Note that although group A *received the* same acceleration *experience* as did group C except for its tilted position no habituation was displayed in the horizontal plane on trial 10 by group A

to a stop with a negative, but subthreshold acceleration lasting 9 5 minutes

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The variance of nystagmus output scores is greater about high output means than about low output means a circumstance that may lead to statistical difficulties Homogeneity of variance was gained by using the logarithms of each output score for analysis The means shown in Fig 4

Associated with these directional characteristics and specificity of nystagmus habituation a counter reflex is sometimes found which may be a factor in habituation It is conceivable that such a compensatory reaction serves to cancel the fundamental or prior response (Fukuda, Hinoki & Tokita, 1958, Guedry & Graybiel 1962) Thus far, this counter response is seen only under rather special experimental conditions Fukuda *et al* (1958) described a counter response (head turning in the chicken) and identified it as the "kinetic labyrinthine reflex", a normal consequence of repeated exposure to angular acceleration Similar events may be identified influencing the human subjective response (Guedry, Cramer & Koella, 1958) A very specific counter-directional or compensatory nystagmus is produced after extended exposure to Coriolis accelerations (Guedry & Graybiel, 1962), a fact also true for subjective reports after even brief exposures (Guedry, Graybiel & Collins 1962) Parenthetically, habituation to Coriolis accelerations does not transfer to angular accelerations in the plane of the lateral canals (Guedry Collins & Graybiel 1964) A prominent counter response or homolateral nystagmus can be induced by unilateral caloric irrigation of the cat (Collins, 1963) Caloric irrigation sometimes perforates the tympanic membranes in the cat (Proctor & Fernandez, 1963), and this could cause aberrations in cooling and nystagmus in an unexpected direction (Jongkees 1948) However, we have noted in one otherwise normal cat a prominent counter nystagmus developed in response to repeated angular accelerations and it clearly commenced before the cessation of an acceleration

The vestibular efferent fibers have also been speculatively offered as a critical link in the habituation process (Fluur & Mendel, 1962 *a*), but efferent functions are still very much a matter of conjecture While there does not appear to be any justification at present for the positive implication of particular structures underlying habituation, explicit description of the variables controlling habituation do provide a framework for a neuro and electrophysiological delineation of the habituation mechanism

ACKNOWLEDGEMENT

The technical assistance of Gerald Burdette is gratefully acknowledged

ZUSAMMENFASSUNG

Eine Gruppe von Katzen wurde einer Serie von Beschleunigungen um eine vertikale Drehungsachse ausgesetzt so dass ein synergetisches Paar der vertikalen Kanäle in der Rotationsebene lag nachher wurden sie mit den Seitenkanälen in der Rotationsebene beobachtet Diese Gruppe wurde mit einer zweiten Gruppe verglichen in welcher nur die Seitenkanäle angeregt wurden und dann mit einer dritten Gruppe in welcher weder die Seitenkanäle noch die Vertikalkanäle angeregt wurden Es wurde gefunden dass die wiederholten Beschleunigungen der vertikalen Kanäle den Nystagmus welcher durch eine Beschleunigung der Seitenkanäle in der Rotationsebene erzeugt wurde, nicht vermindern

TABLE 1. *Covariance analysis for the data from trials 1 and 10*

Source of variation	df	Mean square	F
Adjusted means groups *A*, *B*, *C*	2	0.577	25.087*
Within groups	56	0.023	
Adjusted means groups *A*, *B*	1	0.015	—
Within groups	37	0.028	
Adjusted means groups *A*, *C*	1	1.183	73.938*
Within groups	37	0.016	
Adjusted means groups *B*, *C*	1	0.705	44.062*
Within groups	37	0.016	

* 0.001 level of significance

significantly from groups *A* or *B*, but groups *A* and *B* do not differ from one another. It is conclusively shown that repeated vertical canal stimulation does not reduce nystagmus elicited by stimulation of the lateral canals.

DISCUSSION

These data present clear evidence that no habituation was found to lateral canal stimulation after a synergic pair of vertical canals were repeatedly accelerated. The experiment examined only the simple case in which the two orthogonal planes of stimulation were also canal planes. Habituation of nystagmus may not transfer between other orthogonal planes, but the present data do not bear critically on this aspect. Suffice it to say, that the data do indicate that the plane of rotation must be taken into account when deliberately producing habituation, just as must be done for the direction of the angular acceleration (Crampton, 1962 *a*).

General comment

An adequate explanation for nystagmic habituation has not yet been proffered, but sense-organ fatigue or a peripheral explanation would appear to be ruled out. The exclusion of this factor is based on the findings of Henriksson, Kohut & Fernandez (1961) and Collins (1964) for the cat, and Fluur & Mendel (1962 *a*) for man. It was found that repeated caloric irrigation of one ear produced a nystagmic habituation that was direction-specific (e.g., repeated warm water douching of the right ear produced a habituated nystagmus with a fast phase to the right) and that this habituation would be displayed with other stimulus combinations which would produce a nystagmus of the same direction (e.g., cold water irrigation of the left ear). In other words, habituation may be described as specific to the characteristics of the nystagmus, not to the characteristics of the sense-organ stimulation itself.

SUBSTITUTION D'UN CANAL SEMI-CIRCULAIRE VERTICAL A UN CANAL HORIZONTAL CHEZ LA GRENOUILLE

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On décrit l'opération qui, chez la Grenouille, permet d'innerver la crête ampullaire du canal vertical antérieur avec le nerf ampullaire du canal horizontal. Une fois réalisée la nouvelle innervation, le canal horizontal est remplacé dans son activité tonique par le canal vertical; de plus, la stimulation de celui-ci provoque des réactions qui sont habituellement dues à la stimulation du canal horizontal. Le comportement des grenouilles ainsi opérées conduit en outre aux conclusions suivantes:

1° les courants ampullofuges dans les canaux horizontaux ont en général un pouvoir reflexogène plus faible que les courants ampullopètes.

2° Le nerf ampullaire d'un canal horizontal contient sans doute deux sortes de fibres, les unes participant principalement à la fonction tonique, les autres intervenant surtout lors des stimulations produites par des courants d'endolymphe.

INTRODUCTION

L'élimination d'un canal semi-circulaire horizontal peut être réalisée chez la Grenouille sans porter atteinte aux autres récepteurs vestibulaires par section du nerf am... lle se l...
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termes, nous avons tenté de dissocier les deux fonctions d'un canal semi-circulaire: sa fonction tonique et sa fonction dynamique, celle-ci se manifestant lors d'une stimulation du canal.

Dans ce but, profitant de la facilité avec laquelle le nerf d'un canal semi-circulaire, lorsqu'il a été coupé, régénère sa partie périphérique, nous avons innervé la crête du canal vertical antérieur avec le *nerf du canal horizontal*. Cette opération est rendue possible par la disposition anatomique des ampoules et des nerfs ampullaires de ces deux canaux, accessibles grâce à une perforation du plafond de la bouche.

EXPÉRIENCES ET RÉSULTATS

I. *Description de l'opération*[1]

Après avoir coupé chacun des nerfs ampullaires à son extrémité, on replie le nerf de l'ampoule verticale et on amène sur cette ampoule le nerf du canal

[1] Cette opération est souvent désignée dans la suite par l'expression «opération R» du mot *régénération*.

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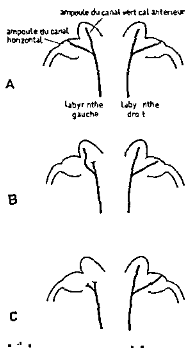


FIG 2 A Innervat

Les animaux temoins chez lesquels les nerfs des deux canaux ont été coupés sans possibilite de regeneration (Fig 2, C) n acquierent pas la reaction « R » et la dissymetrie tonique ne disparait pas chez eux au bout d'un mois, la tendance a tourner vers le cote opere existe toujours, encore tres nette chez les deux tiers d entre eux attenuee chez les autres

III Expériences de contrôle

1) *Section du nerf regeneré*

Il est en general difficile d opérer deux fois la meme oreille lorsqu on ouvre la capsule labyrinthique quelques semaines apres une operation, on la trouve souvent remplie par un tissu conjonctif très vascularise, et les hemorragies qui se produisent alors empechent d avoir une bonne visibilite Cependant quatre fois, chez des grenouilles « R », nous avons pu couper les fibres innervant l ampoule du canal vertical anterieur, dans tous les cas, la reaction caracteristique a disparu apres l operation, et ces grenouilles ont en meme temps retrouve une vive tendance a tourner du cote opere

2) *Operation « R » accompagnee de la suppression des deux canaux correspondants dans l oreille opposee*

Chez quatre grenouilles nous avons realise l operation « R » dans l oreille gauche en meme temps que dans l oreille droite nous coupions le nerf du

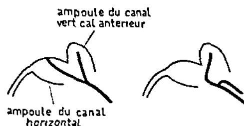


Fig. 1. Innervation du canal vertical antérieur avec le nerf du canal horizontal: réalisation de l'opération.

horizontal (Fig. 1); on cautérise ensuite l'ampoule horizontale pour en détruire la crête; ces précautions sont destinées à éviter que chacun des nerfs ne régénère l'extrémité de ses fibres dans la crête où elles se terminaient auparavant et à favoriser, au contraire, l'allongement et la pénétration des fibres du nerf ampullaire horizontal dans la crête de l'ampoule verticale. L'innervation de cette crête par le nerf du canal horizontal se réalise dans presque tous les cas; elle se manifeste bientôt par ses conséquences fonctionnelles, analogues à celles qu'ont observées Sperry (1943) et Sperry & Miner (1949) à la suite d'interventions semblables sur d'autres récepteurs sensoriels; elle peut également être contrôlée sur des coupes histologiques.

II. *Conséquences fonctionnelles de la nouvelle innervation*

Les grenouilles opérées comme il vient d'être dit ont tout d'abord un comportement qui traduit à la fois l'absence du canal horizontal et celle du canal vertical antérieur; notons en particulier les faits suivants: lorsqu'on projette la tête vers le haut, elle retombe en basculant du côté opéré — signe de l'absence du canal vertical — et très souvent la grenouille s'incurve en même temps de ce côté, puis elle se met parfois à tourner du même côté — signe de l'absence du canal horizontal. Ces grenouilles ont une vive tendance à tourner du côté opéré, comme il arrive toujours après suppression d'un canal *horizontal*. *Cependant, chez la plupart des animaux ayant subi l'opération* « R », une réaction nouvelle et caractéristique (dite réaction « R ») apparaît au bout de 2 semaines environ et atteint son amplitude maximale 3 ou 4 semaines après l'opération: lorsqu'on projette la tête vers le haut, elle retombe en déviant du côté opposé à celui de l'opération; si l'on répète plusieurs fois cet essai, la grenouille s'incurve du même côté de plus en plus fortement et parfois se met à tourner dans ce sens. En même temps, la tendance à tourner du côté opéré s'atténue rapidement; à partir de la 2ᵉ semaine elle a disparu complètement ou presque complètement au bout de 3 ou 4 semaines, et, si ce n'était l'absence toujours perceptible du canal vertical antérieur, ces animaux (que dans la suite nous appellerons *grenouilles* « R ») sembleraient dans leurs déplacements avoir un appareil vestibulaire normal. La nouvelle innervation peut être observée en mettant à nouveau à nu les ampoules du canal horizontal et du canal vertical antérieur

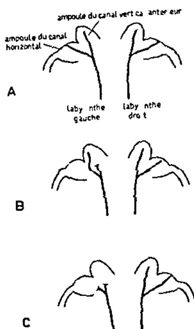


FIG 2 A Innervation normale des canaux horizontaux et des canaux verticaux antérieurs *B* Innervation nouvelle réalisée chez les grenouilles R (opérées dans l'oreille gauche) *C* Grenouilles témoins suppression dans l'oreille gauche du canal horizontal et du canal vertical antérieur

Les animaux témoins chez lesquels les nerfs des deux canaux ont été coupés sans possibilité de régénération (Fig 2 C) n'acquièrent pas la réaction R et la dissymétrie tonique ne disparaît pas chez eux au bout d'un mois la tendance à tourner vers le côté opéré existe toujours encore très nette chez les deux tiers d'entre eux atténuée chez les autres

III *Expériences de contrôle*

1) *Section du nerf régénéré*

Il est en général difficile d'opérer deux fois la même oreille lorsqu'on ouvre la capsule labyrinthique quelques semaines après une opération on la trouve souvent remplie par un tissu conjonctif très vascularisé et les hémorragies qui se produisent alors empêchent d'avoir une bonne visibilité Cependant quatre fois chez des grenouilles « R » nous avons pu couper les fibres innervant l'ampoule du canal vertical antérieur dans tous les cas la réaction caractéristique a disparu après l'opération et ces grenouilles ont en même temps retrouvé une vive tendance à tourner du côté opéré

2) *Opération « R » accompagnée de la suppression des deux canaux correspondants dans l'oreille opposée*

Chez quatre grenouilles nous avons réalisé l'opération « R » dans l'oreille gauche en même temps que dans l'oreille droite nous coupions le nerf du

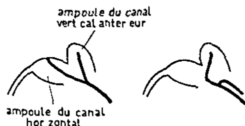


Fig. 1. Innervation du canal vertical antérieur avec le nerf du canal horizontal; réalisation de l'opération.

horizontal (Fig. 1); on cautérise ensuite l'ampoule horizontale pour en détruire la crête; ces précautions sont destinées à éviter que chacun des nerfs ne régénère l'extrémité de ses fibres dans la crête où elles se terminaient auparavant, et à favoriser au contraire l'allongement et la pénétration des fibres du nerf ampullaire horizontal dans la crête de l'ampoule verticale. L'innervation de cette crête par le nerf du canal horizontal se réalise dans presque tous les cas; elle se manifeste bientôt par ses conséquences fonctionnelles, analogues à celles qu'ont observées Sperry (1943) et Sperry & Miner (1949) à la suite d'interventions semblables sur d'autres récepteurs sensoriels; elle peut également être contrôlée sur des coupes histologiques.

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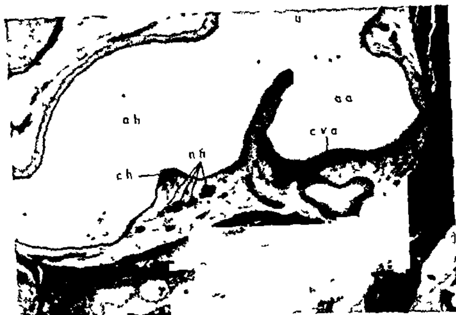


Fig 4 Crêtes ampullaires du canal horizontal et du canal vertical antérieur (coupe horizontale) *u* Utricule *a h* ampoule du canal horizontal *c h* crête ampullaire du canal horizontal *n h* filets nerveux du nerf ampullaire du canal horizontal *a a* ampoule du canal vertical antérieur *c v a* crête ampullaire du canal vertical *antérieur* (42)

horizontal et du canal vertical antérieur et si en meme temps on *détruit* le ganglion de Scarpa pour empecher toute régénération les cretes *dégénèrent* ainsi que les parties périphériques des filets nerveux coupés Deux mois après la section les deux cretes ont disparu l épithelium de la paroi des ampoules a l emplacement des cretes s est entièrement dédifferencié et il est devenu semblable a l épithelium qui forme la paroi de tout le *labyrinthe* (Fig 5) Les filets nerveux du nerf ampullaire horizontal *et* les fibres nerveuses qui se dirigeaient vers les cellules ciliées de la crete ont également tout a fait disparu

Il semble que la destruction des cretes resulte de la *suppression de leur* innervation en d autres termes une crete ne conserve sa structure normale que si elle est innervée et l étude des grenouilles « R » montre que la structure est conservée *meme* si la crete recoit le nerf ampullaire d un autre canal Si l on fait des coupes *dans la tete des grenouilles* R deux mois apres les avoir operées on constate que la *crete ampullaire* du canal horizontal qui n a plus d innervation est détruite *au contraire* la crete du canal vertical antérieur qui est innervée par le *nerf ampullaire* du canal horizontal a une structure normale (Fig 6) L étude des coupes en série permet de suivre le trajet des filets nerveux on voit les fibres du nerf ampullaire horizontal aboutir à l ampoule du canal vertical *antérieur* et penetrer dans la crete de cette ampoule

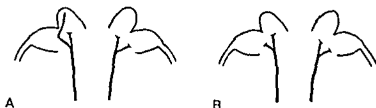


Fig 3 A Dans le labyrinthe gauche nerf du canal horizontal innervant la crête du canal vertical antérieur dans le labyrinthe droit suppression du canal horizontal et du canal vertical antérieur *B* Suppression des deux canaux horizontaux et des deux canaux verticaux antérieurs

canal horizontal et celui du canal vertical anterieur de facon qu ils ne puissent pas regenerer

Apres cette double operation la posture etait normale et le comportement des animaux traduisait l absence des canaux horizontaux (suppression des reactions rotatoires mouvements de manege des deux cotes) et des canaux verticaux anterieurs (absence de la reaction de soutien chute de la tete en avant au cours des deplacements) lorsqu on abandonnait la tete apres l avoir relevee elle retombait souvent en devant d un cote ou de l autre et parfois la grenouille se mettait a tourner indifferemment vers la droite ou vers la gauche

Trois de ces grenouilles au bout d un mois ne tournaient plus que vers *la droite et leur tete apres avoir ete soulevee retombait en devant* systematiquement de ce cote l innervation de la crete anterieure par le nerf du canal horizontal s etait donc realisee (Fig 3 A) Chez l une de ces deux grenouilles nous avons pu couper sur l ampoule anterieure le nerf regenere l animal a retrouve alors le meme comportement qu apres la premiere operation Ce comportement avait persiste sans modification chez la derniere des quatre grenouilles operees des deux cotes chez cet animal qui restait donc prive des deux canaux horizontaux et des deux canaux anterieurs (Fig 3 B) l innervation B ne s etait pas realisee

IV *Controle histologique*

L ampoule du canal horizontal et celle du canal vertical anterieur de bouchant l une a cote de l autre dans l utricule des coupes horizontales dans le labyrinthe d une grenouille permettent d observer la structure et l innervation des cretes ampullaires de ces deux canaux (Fig 4) La crete du canal horizontal qui est verticale se trouve coupee transversalement sous la crete on voit les filets nerveux du nerf ampullaire et l on peut observer les fibres qui issues de ce nerf se dirigent vers les cellules ciliees de la crete La crete du canal vertical anterieur est coupee suivant sa longueur et on la voit tout entiere sur la Fig 4 Les cretes sont peu elevees et leurs deux faces sont sensiblement symetriques les c p l s sont toujours tres retractees sur les preparations parfois elles sont a p ne visibles

Si chez une grenouille n r a ale n c q les nerfs ampullaires du canal



Fig. 6. Grenouille B: crête ampullaire du canal horizontal détruite, crête du canal vertical antérieur ayant une structure normale (coupe horizontale × 45). Comparer avec les Fig. 4 et 5.

	I		II	
	H	AH	H	AH
A				
B				
C				
D				
E				

Fig. 7. Comparaison des réactions postrotatoires. *I*, Grenouilles dont l'appareil vestibulaire est intact. *II*, Grenouilles B. Sens de la rotation: *H*, sens horaire; *AH*, sens antihoraire. Vitesses de rotation: ligne A 120°/s, *B* 35°/s, *C* 13°/s, *D* 6°/s, *E* 3°/s.



Fig. 5. Disparition des crêtes ampullaires du canal horizontal et du canal vertical antérieur deux mois après section des nerfs ampullaires et destruction du ganglion de Scarpa (coupe horizontale 15). Comparer avec la Fig. 4.

V. *Réactions rotatoires des grenouilles possédant la nouvelle innervation*

Chez une grenouille « R » opérée, par exemple, dans l'oreille gauche, le canal horizontal droit est seul stimulé par la rotation dans un plan horizontal et l'on peut s'en assurer en coupant son nerf : toutes les réactions rotatoires se trouvent alors abolies. Cependant l'animal, au repos, n'est pas affecté de la dissymétrie tonique qui résulterait de la suppression pure et simple du canal gauche, puisqu'il ne présente pas de tendance à tourner du côté opéré.

Nous avons examiné les réactions postrotatoires des grenouilles « R » (*aveugles, bien entendu*) *dans les conditions définies précédemment pour* l'étude de ces réactions, et en employant les mêmes vitesses de rotation (Gribenski, 1964).

Les réactions rotatoires des grenouilles « R » sont d'amplitude plus faible que celle des grenouilles normales (Fig. 7), ce qui correspond au fait qu'un seul canal horizontal est stimulé au lieu de deux. En outre, ces réactions ne sont pas tout à fait équivalentes dans les deux sens ; si les animaux ont subi l'opération « R » dans l'oreille gauche, les réactions postrotatoires dirigées vers la gauche ont, le plus souvent, une amplitude un peu plus grande et un seuil un peu plus faible que les réactions dirigées vers la droite.

Or les réactions vers la gauche sont dues à des courants d'endolymphe ampullopètes dans le canal horizontal droit et les réactions vers la droite à des courants ampullofuges dans le même canal. Par conséquent, malgré

rotation uniforme ne depasse pas 70°/s En effet pour cette valeur de la vitesse, la stimulation par un courant ampullofuge fait disparaitre toute activite electrique sur le nerf une stimulation plus intense dans ce sens ne peut donc pas produire un effet plus important L accroissement d activite du a un courant ampullopete n est pas limite de la meme facon la reponse electrique dans ce cas peut depasser la valeur de l activite de repos

D apres ces donnees on pourrait penser que une fois la dissymetrie tonique annulee les deux sens de stimulation vont donner naissance a des reactions d amplitude egale si les stimuli sont de faible intensite Cependant l etude des reactions rotatoires chez les grenouilles « R » montre qu il n en est en general pas ainsi au contraire les courants ampullopetes se montrent plus efficaces que les courants ampullofuges notamment au voisinage du seuil c est a dire pour les faibles stimulations

Nous ne pensons pas que ces faits soient en contradiction avec la symetrie des reponses electriques observee par Ledoux En effet un courant ampullopete et un courant ampullofuge identiques — au sens pres — du point de vue mecanique peuvent ne pas etre des stimuli equivalents meme s ils determinent des reponses electriques egales en valeur absolue en d autres termes une augmentation et une diminution de l activite electrique du nerf si elles ont globalement la meme valeur absolue n affectent peut etre pas symetriquement toutes les fibres a plus forte raison ne pouvons nous pas attendre qu elles retentissent symetriquement sur le systeme reflexe

Notons encore que l inegalite entre les reactions dues aux courants ampullopetes et aux courants ampullofuges est plus ou moins marquee selon les individus chez certains d entre eux elle est peu sensible

Enfin il se peut qu il existe une difference entre les grenouilles « R » et les grenouilles normales quant aux reponses d un canal horizontal stimule par la rotation en effet les influx efferents reçus par ce canal ne sont sans doute pas identiques dans les deux cas (Schmidt 1963)

4° Le comportement des grenouilles « R » n est pas tout a fait constant La majorite de ces animaux presentent la reaction caracteristique (reaction « R ») tres regulierement et sont completement symetriques du point de vue tonique Mais quelques uns avec une symetrie tonique parfaite presentent la reaction R de facon irreguliere tandis que d autres qui manifestent la reaction R tout a fait regulierement restent affectes d une legere dissymetrie tonique Ces differences se maintiennent avec le temps On ne peut en proposer qu une explication pensons nous c est que les fibres du nerf ampullaire ne jouent pas toutes le meme role sans doute certaines de ces fibres ont elles plutot une fonction tonique qui s exprime par l action permanente du canal semi circulaire d autres fibres au contraire doivent intervenir surtout — ou seulement — a l occasion d une stimulation du canal la regeneration qui se produit chez les grenouilles « R » pourrait aboutir selon les cas a une predominance des unes ou des autres Une telle interpretation peut s accorder avec les observations de Gernandt (1949) sur l activite electrique des fibres du nerf vestibulaire chez le Chat

l'absence de dissymétrie tonique, les réactions dues aux courants ampullopètes l'emportent sur celles que déterminent les courants ampullofuges.

DISCUSSION ET CONCLUSION

1° Chez une grenouille « R » opérée du côté *gauche*, la *réaction « R »* se produit vers la droite. Déviation de la tête et incurvation de l'animal vers la droite sont habituellement des réactions dues à la stimulation du canal horizontal gauche par un courant d'endolymphe ampullopète — stimulation qui accroît l'activité électrique du nerf ampullaire horizontal ; ces réactions *répondent ici à la stimulation du canal vertical antérieur par le courant* ampullofuge que crée dans ce canal la chute de la tête. Or lorsque la crête du canal vertical a son innervation normale, un tel courant produit un accroissement de l'activité électrique du nerf ampullaire de ce canal (Ledoux, 1948) ; on peut penser que, chez les grenouilles « R », il produit aussi un accroissement d'activité sur le nerf aboutissant à la crête du canal vertical, c'est-à-dire ici le nerf ampullaire du canal horizontal ; ainsi se réaliseraient par la stimulation du canal vertical antérieur les réactions habituellement dues à la stimulation du canal horizontal par un courant ampullopète.

2° La disparition, chez les grenouilles « R », de la tendance à tourner vers le côté opéré — tendance qui reste nette habituellement lorsque l'innervation caractéristique de ces animaux ne se réalise pas — montre que l'action tonique du canal horizontal de l'oreille intacte peut être équilibrée par celle du canal vertical antérieur de l'oreille opérée ; ainsi ce canal remplace dans sa fonction tonique le canal horizontal supprimé. Or il est probable que la symétrie tonique, chez l'animal normal, résulte d'un équilibre entre les activités électriques des nerfs correspondant aux canaux horizontaux opposés ; on peut donc penser que l'activité électrique de repos du nerf ampullaire horizontal est sensiblement la même quand ce nerf est dévié pour innerver la crête du canal vertical que lorsqu'il innerve normalement celle du canal horizontal.

Il peut même arriver que l'action tonique du canal vertical opéré l'emporte sur celle du canal horizontal du labyrinthe opposé ; nous avons en effet observé des grenouilles « R » qui avaient tendance à tourner spontanément vers le côté intact, comme si l'activité électrique du nerf ampullaire du canal horizontal était plus grande dans l'oreille opérée que dans l'oreille intacte.

3° *On sait que*, s'agissant des canaux horizontaux, un courant d'endolymphe ampullopète détermine un accroissement de l'activité électrique du nerf ampullaire, un courant ampullofuge une inhibition de cette activité. Selon Ledoux (1958), pour les stimuli de même valeur, les réponses électriques globales — accroissement ou diminution, selon le cas, de l'intégrale des décharges élémentaires — ont la même valeur absolue dans les deux sens si les stimuli n'ont pas une intensité trop élevée, c'est-à-dire si, dans les conditions de décélération que réalisent nos expériences, la vitesse de

rotation uniforme ne dépasse pas 70°/s. En effet, pour cette valeur de la vitesse la stimulation par un courant ampullofuge fait disparaître toute activité électrique sur le nerf; une stimulation plus intense dans ce sens ne peut donc pas produire un effet plus important. L'accroissement d'activité dû à un courant ampullopète n'est pas limité de la même façon: la réponse électrique, dans ce cas, peut dépasser la valeur de l'activité de repos.

D'après ces données, on pourrait penser que, une fois la dissymétrie tonique annulée, les deux sens de stimulation vont donner naissance à des réactions d'amplitude égale si les stimuli sont de faible intensité. Cependant l'étude des réactions rotatoires chez les grenouilles « R » montre qu'il n'en est en général pas ainsi; au contraire, les courants ampullopètes se montrent plus efficaces que les courants ampullofuges, notamment au voisinage du seuil, c'est-à-dire pour les faibles stimulations.

Nous ne pensons pas que ces faits soient en contradiction avec la symétrie des réponses électriques observée par Ledoux. En effet, un courant ampullopète et un courant ampullofuge identiques — au sens près — du point de vue mécanique peuvent ne pas être des stimuli équivalents, même s'ils déterminent des réponses électriques égales en valeur absolue; en d'autres termes, une augmentation et une diminution de l'activité électrique du nerf, si elles ont globalement la même valeur absolue, n'affectent peut-être pas symétriquement toutes les fibres; à plus forte raison, ne pouvons-nous pas attendre qu'elles retentissent symétriquement sur le système réflexe.

Notons encore que l'inégalité entre les réactions dues aux courants ampullopètes et aux courants ampullofuges est plus ou moins marquée selon les individus; chez certains d'entre eux, elle est peu sensible.

Enfin, il se peut qu'il existe une différence entre les grenouilles « R » et les grenouilles normales, quant aux réponses d'un canal horizontal stimulé par la rotation; en effet, les influx efférents reçus par ce canal ne sont sans doute pas identiques dans les deux cas (Schmidt, 1963).

4° Le comportement des grenouilles « R » n'est pas tout à fait constant. La majorité de ces animaux présentent la réaction caractéristique (réaction « R ») très régulièrement et sont complètement symétriques du point de vue tonique. Mais quelques-uns, avec une symétrie tonique parfaite, présentent la réaction « R » de façon irrégulière, tandis que d'autres, qui manifestent la réaction « R » tout à fait régulièrement, restent affectés d'une légère dissymétrie tonique. Ces différences se maintiennent avec le temps. On ne peut en proposer qu'une explication, pensons-nous: c'est que les fibres du nerf ampullaire ne jouent pas toutes le même rôle; sans doute, certaines de ces fibres ont-elles plutôt une fonction tonique, qui s'exprime par l'action permanente du canal semi-circulaire; d'autres fibres, au contraire, doivent intervenir surtout — ou seulement — à l'occasion d'une stimulation du canal. La régénération qui se produit chez les grenouilles « R » pourrait aboutir, selon les cas, à une prédominance des unes ou des autres. Une telle interprétation peut s'accorder avec les observations de Gernandt (1949) sur l'activité électrique des fibres du nerf vestibulaire chez le Chat.

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LES TESTS D'ATTEINTE AUDITIVE CORTICALE ET CENTRALE

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Travail du Service de Neuro-Chirurgie (Dir Prof David), Hopital de la Pitie et au Service O R L (Dr Maspetiol), Hopital Bichat Paris

Dans 48 observations neurologiques on a etudie les tests tonals et vocaux d'atteinte auditive corticale et centrale Les resultats obtenus ont ete compares avec les conclusions anterieures sur leur valeur semiologique respective L'etude critique de ces resultats a confirme l'interet clinique de ces deux types de tests

Pour les tests du type tonal le temps de reaction auditive lorsqu'il est prolonge traduit bien une lesion corticale le test d'integration bi auriculaire lorsqu'il est perturbe temoigne d'une lesion sous corticale ou du tronc cerebral Le Relapse du type II est le temoin d'une lesion du tronc cerebral Les SAI tres eleves s'observent dans les lesions corticales et les lesions du tronc cerebral

Pour les tests vocaux on peut avec Bocca distinguer les tests corticaux voix filtree voix accelcree les tests centraux voix interrompue voix alternee

Dans l'ensemble tests tonals et tests vocaux donnent des resultats concordants Les cas discordants sont l'exception

L'etude des troubles auditifs d'origine corticale ou centrale s'est enrichi depuis ces dernieres annees de deux nouvelles methodes d'examen 1) les tests du type tonal que nous avons personnellement etudies, 2) les tests sensibilises du type vocal misent au point par Bocca Agazzi et Calearo

Le but de ce travail base sur 48 nouvelles observations otoneurologiques, est de faire une etude critique et comparative de la valeur semiologique des tests tonals et vocaux d'atteinte corticale et centrale

MATERIEL D'ETUDES

Toutes les observations qui sont a la base de ce travail ont été prises dans le Service de Neuro-Chirurgie du Prof David a l'Hopital de la Pitie Chaque observation comporte l'étude des deux types de tests tonals et vocaux De plus nous n'avons retenu que les observations pour les-

Travail réalisé grâce à une subvention de l'Institut National d'Hygiene (Dr Aujaleu

SUMMARY

Here is described the operation which makes possible, in the frog, to innervate the crista ampullaris of the anterior vertical canal with the ampullary nerve of the horizontal canal After having realized the new innervation, the horizontal canal is replaced in its tonic activity by the vertical one, further, the stimulation of the vertical canal provokes reactions which normally result from the stimulation of the horizontal one Besides, the behaviour of the frogs operated in this way leads us to the following conclusions:

1 The ampullofugal currents in the horizontal canals generally have a reflexogenic action weaker than that of the ampullopetal currents

2 The ampullary nerve of a horizontal canal probably contains two kinds of fibers, one taking part mainly in the tonic function of the canal, the other participating especially during the stimulation produced by the flow of endolymph

ZUSAMMENFASSUNG

Wir beschreiben die Operation, welche beim Frosch die Innervation der Crista ampullaris des vorliegenden vertikalen Kanals mit dem ampullaren Nerv des horizontalen Kanals ermoglicht Sobald die neue Innervation hergestellt ist, wird die tonische Tatigkeit des horizontalen Kanals durch den vertikalen Kanal ersezt Ausserdem bewirkt die Stimulation des letzteren Reaktionen, welche gewohnlich durch die Stimulation des horizontalen Kanals hervorgerufen werden Das Benehmen der *auf solche Weise operierten Frosche fuhrt uns ausserdem zu folgenden* Schlussfolgerungen

1 Die ampullofugen Stromungen in den horizontalen Kanalen haben gewohnlich *eine schwachere reflexogene Kraft als die ampullopeten Stromungen*

2 Der ampullare Nerv eines horizontalen Kanals besitzt hochstwahrscheinlich zwei Arten von Fasern Die einen beteiligen sich hauptsachlich an der tonischen Funktion, *die anderen machen sich besonders bei Stimulationen bemerkbar,* welche von Endolymphstromungen hervorgerufen werden

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7, rue Coëtlogon Paris (VIe) France

Reçu le 10 mars 1964

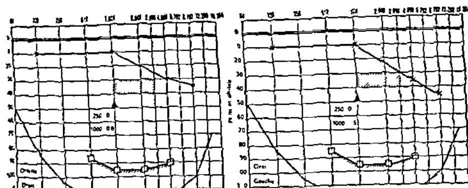


Fig 1

TRA = 250	
Vocale simple	100 %
Voix interrompue	100 %
Voix filtrée	80 %
Voix accélérée	100 %
Voix alternée	100 %

TRA 200

TRA = 200	
Vocale simple	100 %
Voix interrompue	90 %
Voix filtrée	60 %
Voix accélérée	70 %
Voix alternée	100 %

Le seuil différentiel d'intensité *diminue* en présence d'un son controlatéral *continue* et de *fréquence différente* surtout plus grave Pour reprendre l'exemple précédent où le SAI pour la fréquence 1000 était à 1 db ce SDI passe à 0 8-0 6 db lorsque sur l'oreille opposée on émet la fréquence 250 également à une intensité faible + 20 db Dans ce cas le son controlatéral de fréquence différente a produit un effet de facilitation

Le TIB donne une réponse pathologique lorsque le SDI n'est pas modifié en présence d'un son controlatéral soit de même fréquence soit de fréquence différente

3) *Le test du contrôle central de la fatigue auditive* (9)

C'est un test *d'atteinte centrale* Il a la même valeur sémiologique que le *TIB* Leurs réponses sont concordantes ainsi nous n'avons recours à ce test que dans les cas exceptionnels où le TIB n'a pu être recherché pas de perception de la modulation réponses imprécises du sujet

Dans ce *test chez un* sujet normal on constate que la présence d'un bruit blanc controlatéral de faible intensité diminue la fatigue auditive (technique de Pesser) diminution portant et sur la perte en décibels et sur la durée de récupération La non modification de la fatigue auditive par un son controlatéral est pathologique et traduit une atteinte auditive centrale

4) *Etude du Relapse (détérioration du seuil tonal)*

C'est un test interrogeant les voies auditives au niveau du *tronc cérébral* Il existe deux types de relapse Le relapse du type I c'est le relapse classique relapse peu important de 10 à 20 db et sans grand intérêt Car con

quelles les données cliniques, opératoires ou autopsiques permettaient une certaine localisation de la lésion

Ces 48 observations comportent

21 lésions temporales dont 8 glioblastomes ou astrocytomes 2 méningiomes 3 syndromes temporal d'origine vasculaire 4 syndromes temporal d'origine traumatique 4 aphasies isolées d'origine vasculaire

13 lésions corticales non temporales dont 3 tumeurs frontales ou occipitales avec stase papillaire 1 hématome frontal sous dural chronique

8 épilepsies, dont 3 épilepsies temporales

6 lésions du tronc cérébral, dont 3 gliomes du tronc cérébral 2 d'origine traumatique, 1 d'origine vasculaire

LES TESTS TONALS ET VOCAUX D'ATTEINTE CORTICALE ET CENTRALE

Nous ne ferons que rappeler très brièvement ces différents tests

a) Les tests tonals

Ces tests comportent l'étude du temps de réaction auditive (TRA) le test d'intégration bi-auriculaire (TIB) le test du contrôle central de la fatigue auditive l'étude du Relapse

1) *Le temps de réaction auditive*

C'est un *test d'atteinte corticale* (7 8 10, 11) Il doit être considéré comme pathologique, soit en cas de prolongation *unilatérale* d'un TRA par rapport à celui de l'oreille opposée soit en cas de prolongation *bilatérale* par comparaison avec le temps de réaction visuel celui-ci est classiquement plus long d'un $1/_{3}$ environ que le TRA notion classique qui est parfaitement exacte pour une lampe à incandescence mais non retrouvée en utilisant une lampe à flasch où les deux temps auditifs et visuels paraissent identiques

2) *Le test d'intégration bi-auriculaire*

C'est un *test d'atteinte centrale* (sous cortical ou tronc cérébral) (7 8 10 11) Il est basé sur la recherche de processus d'inhibition et de facilitation du seuil différentiel d'intensité (SAI) en présence d'un son controlatéral de *faible intensité* (Chocholle) Le SAI augmente en présence d'un son controlatéral de même fréquence Si le SDI pour la fréquence 1000 est de 1 décibel, celui-ci passe par exemple à 1 db 4 lorsque sur l'oreille opposée on émet *cette même fréquence 1000* à une intensité faible + 20 db pour éliminer une action controlatérale Dans ce cas le son controlatéral de même fréquence a produit un effet *d'inhibition* sur le SDI

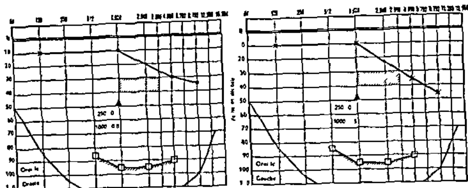


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Voix interrompue	100 %
Voix filtrée	80 %
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Voix alternée	100 %

TRA = 200

TRA = 200	
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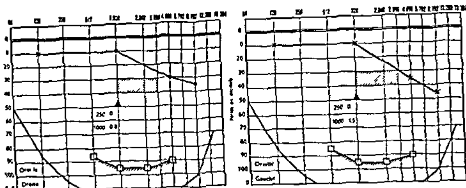


FIG. 1

TRA = 200

TRA = 250	
Vocale simple	100 %
Voix interrompue	100 %
Voix filtrée	80 %
Voix accélérée	100 %
Voix alternée	100 %

TRA = 700	
Vocale simple	100 %
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Voix filtrée	60 %
Voix accélérée	70 %
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trairement aux notions classiques il n'est pas pathognomonique de lésions cochléaires. Il s'observe également dans les lésions du tronc cérébral et central. Le relapse du type II est le seul qui nous intéresse : il est très important c'est en 1 minute une perte du seuil tonal de 40 à 100 db ; il est peut-on dire pathognomonique d'une lésion du tronc cérébral et dans ces lésions il est très fréquent, on le constate dans les $^3/_4$ des cas.

En dehors de ces différents tests et toujours dans le domaine de l'audiométrie tonale il convient de souligner l'intérêt de la recherche : *a)* des seuils différentiels d'intensité pour différentes fréquences. Des SDI très élevés au-dessus de 3 traduisent une lésion le plus souvent des aires auditives, mais parfois également du tronc cérébral. *b)* De l'épreuve de Weber. Dans certaines lésions corticales ou centrales on peut constater à titre exceptionnel d'ailleurs un Weber paradoxal, c'est-à-dire latéralisé sur l'oreille la plus sourde, et cela en dehors de tout élément de transmission. Nous avons insisté antérieurement sur ce Weber paradoxal (12).

Les tests vocaux de Bocca, Agazzi et Calearo

Comme pour les tests tonals nous ne ferons que rappeler ces différents tests ; le lecteur voudra bien se reporter aux travaux de ces auteurs (1-6). Les tests vocaux comportent des tests corticaux et des tests centraux.

b) Tests corticaux

Test de la voix filtrée (VF). En utilisant un filtre passe-bas 800 V D un sujet normal obtient une intelligibilité de 90 à 100% pour des phrases émises à une intensité de +40 db.

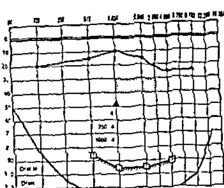
Test de la voix accélérée (VA). Les phrases sont émises toujours à une intensité de +40 db mais à une vitesse accélérée (250 mots à la minute). Dans ces conditions, pour un sujet normal l'intelligibilité est de 90 à 100%.

c) Test centraux

Test de la voix interrompue (VI). Un interrupteur automatique permet d'interrompre le stimulus vocal (phrases à +40 db) de 1 à 10 fois par seconde avec un rapport *message silence constant égal à 1*. Pour un sujet normal en utilisant 10 interruptions par seconde on obtient 100% d'intelligibilité.

Test de la voix alternée (VAL). Le message vocal (liste de phrases à 40 db) passe alternativement d'une oreille à l'autre : chaque oreille ne reçoit que la moitié du message. *Pour un sujet normal* l'intelligibilité de la VAL reste toujours à 100% quelque soit la fréquence d'alternance. En pratique on utilise des fréquences d'alternance allant de 2 à 20 par seconde. Mais c'est le plus souvent avec des alternances de 3 à 6 par secondes que l'on observe les troubles de l'intelligibilité (Calearo).

Ce test d'après Bocca est surtout altéré dans les lésions du tronc cérébral



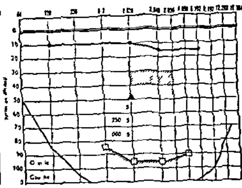


Fig. 2

TRA = 220 TRA = 180 TRA = 200

Vocal simple	30 db	100 %
Voix interrompue	30 db	40 %
Voix filtrée	30 db	10 %
Voix accélérée	30 db	20 %
Voix alternée	30 db	100 %

Vocale simple	100 %
Voix interrompue	60 %
Voix filtrée	30 %
Voix accélérée	50 %
Voix alternée	100 %

ÉTUDE DES RÉSULTATS OBTENUS PAR LES TESTS TONALS ET VOCAUX

(48 observations)

Pour faciliter l'interprétation des résultats nous rappelerons pour chaque type de lésions et pour chaque test les réponses que l'on « doit » obtenir, *en principe* compte tenu des conclusions antérieures sur la valeur sémiologique de ces tests (7 8 3 4 5)

Étude des réponses obtenues par les tests tonals

1 *Lésions corticales temporales*

En principe en cas de lésion corticale superficielle, seul le TRA doit être perturbé en cas de lésion corticale à extension profonde, le TRA *et le TIB* doivent également être perturbés Pour la simplification de la présentation nous ne parlerons pas du test du contrôle central de la fatigue auditive qui nous l'avons vu a la même signification que le TIB et qui n'a été recherché que dans les cas exceptionnels où le TIB donnait des réponses imprécises

a) Le TRA était prolongé 15 fois sur les 21 observations ce qui représente déjà un pourcentage élevé *De plus* sur les 6 cas avec TRA normal dans 4 cas il s'agissait d'aphasie sensorielle d'origine vasculaire sans autre signe neurologique Rien n'autorise ici à suspecter une atteinte des aires auditives Par contre dans deux cas les réponses du TRA étaient en désaccord avec la clinique Les conclusions tirées de cette épreuve étaient donc erronées (1 syndrome temporal d'origine vasculaire et surtout, un glioblastome temporal antérieur gauche)

b) Pour le TIB on ne peut juger de sa valeur que dans les cas où l'on peut affirmer l'extension ou non en profondeur. Dans 6 cas où la lésion était certainement superficielle sans extension profonde (4 aphasies, 2 méningiomes) le TIB était normal dans tous les cas. Dans 8 cas de tumeurs *glioblastome ou astrocytome* où l'extension profonde était certaine 7 fois le TIB était perturbé.

2) *Lésions corticales non temporales*

En principe TRA et TIB doivent donner des réponses normales à l'exception des cas avec hypertension IC: il existe alors souvent une *prolongation* bilatérale des TRA.

Le TRA était normal 9 fois sur 13 cas. Il était prolongé dans 4 cas mais en fait dans un seul cas le TRA a donné une réponse erronée (tumeur occipitale sans hypertension) car dans les 3 autres cas avec TRA prolongé il coexistait une HIC.

Le TIB était normal 11 fois sur les 13 cas. Dans les 2 cas où le TIB était paradoxalement perturbé il s'agissait dans un cas d'une tumeur pariéto occipitale, dans le 2e cas d'une tumeur rétro-rolandique avec troubles aphasiques discrets. Dans ces deux observations il convient de noter qu'il était difficile de limiter l'extension exacte de la lésion.

3) *Epilepsie: 8 cas*

En principe, même en cas d'épilepsie temporale, le TRA et le TIB donnent des réponses normales. Dans les 8 cas les réponses des deux tests étaient en effet toutes normales.

4) *Lésions du tronc cérébral: 6 cas*

En principe le TRA doit être normal en dehors des cas où il coexiste une HIC. Par contre le TIB doit être altéré et le Relapse du type II doit être fréquemment observé.

Le TRA était normal 5 fois sur 6. Dans la seule observation où le TRA était prolongé cette réponse était erronée car en désaccord avec la clinique: il s'agissait en effet d'un gliome du tronc cérébral mais sans HIC.

Le TIB était perturbé 4 fois sur 6 (3 gliomes, 1 syndrome vasculaire), normal dans 2 cas (2 syndromes traumatiques).

Relapse du type II était présent 4 fois.

Réponses obtenues par les tests vocaux

1) *Lésions corticales temporales*

En principe d'après Bocca dans les lésions temporales superficielles on observe une altération controlatérale de la VF et de la VA. Dans les

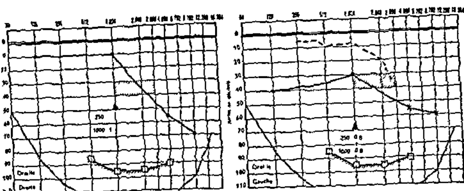


Fig 3

TRA = 130 | TRU = 130 | TRA = 130

Vocale simple	100 %
Voix interrompue	70 %
Voix filtrée	70 %
Voix accélérée	100 %
Voix alternée	100 %

Vocale simple	100 %
Voix interrompue	50 %
Voix filtrée	90 %
Voix accélérée	100 %
Voix alternée	100 %

lésions temporales profondes se surajoutent des altérations de la VI plus rarement de la VAT

a) Dans 11 observations sur les 21, les réponses de ces tests ont été en accord avec les notions sémiologiques mises en évidence par Bocca et que nous venons d'énoncer De plus, en accord avec les constatations de cet auteur, la voix filtrée est plus souvent altérée que le VA Par contre elle ne peut pas être toujours recherchée, notamment en cas de chute sur les fréquences aigues Les troubles de l'intelligibilité sont le plus souvent controlatéraux à la lésion temporale

b) Dans 10 cas, par contre les réponses obtenues n'ont pas correspondu au schéma sémiologique Ces cas méritent d'être discutés

Dans 4 cas tous les tests vocaux étaient altérés et également sur les 2 oreilles Il s'agissait de 4 observations d'aphasie sensorielle isolée d'origine vasculaire Les troubles bilatéraux de l'intelligibilité mis en évidence par ces tests étaient secondaires non pas à des troubles auditifs corticaux, mais aux troubles aphasiques

Dans 4 cas différentes épreuves vocales étaient altérées, mais ces altérations ne correspondaient pas au schéma sémiologique proposé C'est ainsi que dans une observation de méningiome il existait des troubles de la VI alors que les tests corticaux étaient normaux A l'inverse dans deux cas de tumeur (glioblastome et astrocytome) dont l'extension en profondeur était certaine seule la VF était altérée ce qui faisait conclure, à tort à une lésion corticale superficielle

Il convient cependant de souligner que dans ces 4 observations, les tests vocaux n'ont cependant pas été sans intérêt S'il y a eu erreur dans le diagnostic topographique de la lésion, ces tests ont, cependant, pu mettre

en évidence une lésion du système nerveux central ce que les épreuves classiques d'audiométrie tonale et vocale sont bien incapables de faire.

Dans 2 cas par contre, tous les tests vocaux étaient normaux et en désaccord avec la clinique. Les réponses étaient donc erronées.

2) Lésions corticales non temporales

En principe, tous les tests vocaux doivent donner des réponses normales à l'exception des cas où il existe une HIC qui peut s'accompagner d'altérations des tests du type cortical.

Sur ces 13 observations, 8 fois les tests vocaux étaient normaux. Sur les 5 cas avec des tests paradoxalement perturbés, 2 cas seulement doivent être considérés comme ayant des réponses erronées et inexplicables, car les 3 autres cas s'accompagnaient d'HIC : il s'agissait d'altération de la VF.

3) *Épilepsies — 8 cas dont 3 épilepsies temporales*

En principe, les tests vocaux doivent être normaux en dehors des épilepsies temporales où les tests du type cortical sont altérés.

Les faits sont confirmés dans 2 épilepsies temporales : altération d'ailleurs bilatérale des tests corticaux ; dans 4 épilepsies non temporales tous les tests sont normaux.

Par contre dans deux observations les réponses des tests étaient erronées par rapport au diagnostic clinique : 1 épilepsie temporale avec altération de la VI ; 1 épilepsie non temporale (petit mal) où seule la VI était altérée.

4) *Lésions du tronc cérébral — 6 cas*

En principe, seuls les tests du type central et spécialement la VAT doivent être altérés avec les restrictions habituelles en cas d'HIC pour les tests corticaux.

Sur ces 6 observations, 3 cas répondent parfaitement à ce schéma ; 3 cas donnent des réponses non concordantes avec ce schéma, dont 2 cas de syndrome d'origine traumatique (les tests tonals étaient également normaux) mais en fait dans un seul cas (gliome) les tests vocaux avaient donné des réponses erronées, puisque normales.

Valeur séméiologique des tests tonals et vocaux

Les résultats obtenus dans ces 48 observations viennent confirmer la valeur séméiologique de ces différents tests. En effet, le nombre de réponses franchement erronées est de 6 pour le TRA, de 3 pour le TIB et de 11 cas pour l'ensemble des cas vocaux.

Il est possible d'apporter quelques précisions sur la valeur séméiologique de ces tests en tenant compte et des travaux antérieurs et des résultats obtenus dans les observations objets de ce travail.

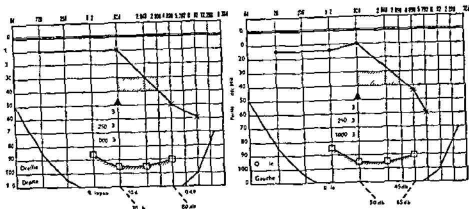


Fig. 4

TRA 150		TRL = 200	TRA 150	
Vocale simple	100 %		Vocale simple	100 %
Voix interrompue	10 %		Voix interrompue	10 %
Voix filtrée	80 %		Voix filtrée	[illegible]
Voix accélérée	100 %		Voix accélérée	100 %
Voix alternée 6 à 8 IS	0 %		Voix alternée 6 à 8 IS	0 %

1) *Le TRA* lorsqu'il est altéré traduit une lésion des aires auditives. La prolongation est soit unilatérale généralement homolatérale soit bilatérale. Il est donc difficile d'après ce test de préciser le côté de la lésion.

A cette règle générale un TRA prolongé traduit une lésion temporale, il convient d'apporter certaines restrictions. Les TRA sont généralement prolongés pour les 2 oreilles en cas HIC et parfois dans les atrophies cérébrales. Les TRA sont toujours très prolongés en cas de presbyacousie. L'altération de ce test nécessite des lésions neurologiques relativement importantes puisque les TRA sont normaux dans les épilepsies temporales.

2) *Le test d'intégration bi auriculaire*. Les réponses pathologiques s'observent dans les lésions centrales soit sous cortical soit du tronc cérébral.

Par ce test il n'est pas possible de distinguer entre lésion sous corticale et lésion du tronc cérébral. On pourrait penser qu'une lésion du tronc cérébral donne des troubles bilatéraux du TIB tandis qu'une lésion sous corticale donne un trouble unilatéral de ce test. L'expérience montre qu'il n'en est rien. La seule précision que l'on puisse apporter est qu'un trouble unilatéral de ce test est en règle homolatérale à la lésion. Ce caractère homolatéral n'est qu'apparent car dans le TIB le facteur actif est en fait le son controlatéral, le SAI de l'oreille homolatérale n'ayant qu'un rôle passif.

3) *Le test du contrôle central de la fatigue* a, rappelons le, la même valeur que le TIB, aussi n'est-il recherché qu'exceptionnellement.

4) *Le Relapse du type II* est très fréquent dans les lésions du tronc cérébral.

5) La constatation de seuil différentiel d'intensité très élevé au dessus de 3 est souvent le fait de lésions corticales mais parfois aussi de lésions du tronc cérébral.

en évidence une lésion du système nerveux *central ce que les épreuves classiques d'audiométrie tonale et vocale sont bien incapables de faire*.

Dans 2 cas, par contre, tous les tests vocaux étaient normaux et en désaccord avec la clinique. Les réponses étaient donc erronées.

2) Lésions corticales non temporales

En principe, tous les tests vocaux doivent donner des réponses normales à l'exception des cas où il existe une HIC qui peut s'accompagner d'altérations des tests du type cortical.

Sur ces 13 observations, 8 fois les tests vocaux étaient normaux. Sur les 5 cas avec des tests paradoxalement perturbés, 2 cas seulement doivent être considérés comme ayant des réponses erronées et inexplicables, car les 3 autres cas s'accompagnaient d'HIC, il s'agissait d'altération de la VI.

3) Épilepsies — 8 cas dont 3 épilepsies temporales

En principe, les tests vocaux doivent être normaux, en dehors des épilepsies temporales où les tests du type cortical sont altérés.

Les faits sont confirmés dans 2 épilepsies temporales, altération d'ailleurs bilatérale des tests corticaux; dans 4 épilepsies non temporales, tous les tests sont normaux.

Par contre, dans deux observations, les réponses des tests étaient erronées par rapport au diagnostic clinique: 1 épilepsie temporale avec altération de la VI; 1 épilepsie non temporale (petit mal) où seule la VI était altérée.

4) Lésions du tronc cérébral — 6 cas

En principe, seuls les tests du type central et spécialement la VAI doivent être altérés, avec les restrictions habituelles en cas d'HIC pour les tests corticaux.

Sur ces 6 observations, 3 cas répondent parfaitement à ce schéma; 3 cas donnent des réponses non concordantes avec ce schéma, dont 2 cas de syndrome *d'origine traumatique* (les tests tonals étaient également normaux), mais en fait dans un seul cas (gliome) les tests vocaux avaient donné des réponses erronées puisque normales.

Valeur séméiologique des tests tonals et vocaux

Les résultats obtenus dans ces 48 observations viennent confirmer la valeur séméiologique de ces différents tests. *En effet, le nombre de réponses* franchement erronées est de 6 pour le IRA, de 3 pour l'IIB et de 11 cas pour l'ensemble des cas vocaux.

Il est possible d'apporter quelques précisions sur la valeur séméiologique de ces tests en tenant compte et des travaux antérieurs et des résultats obtenus dans les observations objets de ce travail.

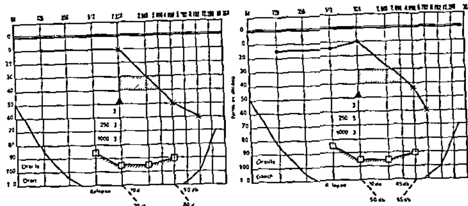


Fig. 4

TRA = 150		TRL = 200	TRA = 150	
Vocal simple	100 %		Vocal simple	100 %
Voix interrompue	10 %		Voix interrompue	10 %
Voix filtrée	80 %		Voix filtrée	70 %
Voix accélérée	100 %		Voix accélérée	100 %
Voix alternée 6 à 8 IS	0 %		Voix alternée 6 à 8 IS	0 %

1) *Le TRA* lorsqu'il est altéré traduit une lésion des aires auditives. La prolongation est, soit unilatérale, généralement homolatérale, soit bilatérale. Il est donc difficile d'après ce test, de préciser le côté de la lésion.

A cette règle générale: un TRA prolongé traduit une lésion temporale, il convient d'apporter certaines restrictions. Les TRA sont généralement prolongés pour les 2 oreilles en cas HIC et parfois dans les atrophies cérébrales. Les TRA sont toujours très prolongés en cas de presbyacousie. L'altération de ce test nécessite des lésions neurologiques relativement importantes puisque les TRA sont normaux dans les épilepsies temporales.

2) *Le test d'intégration biauriculaire*. Les réponses pathologiques s'observent dans les lésions centrales soit sous cortical soit du tronc cérébral.

Par ce test, il n'est pas possible de distinguer entre lésion sous corticale et lésion du tronc cérébral. On pourrait penser qu'une lésion du tronc cérébral donne des troubles bilatéraux du TIB tandis qu'une lésion sous corticale donne un trouble unilatéral de ce test. L'expérience montre qu'il n'en est rien. La seule précision que l'on puisse apporter est qu'un trouble unilatéral de ce test est en règle homolatéral à la lésion. Ce caractère homolatéral n'est qu'apparent car dans le TIB le facteur actif est en fait le son controlatéral, le SAI de l'oreille homolatérale n'ayant qu'un rôle passif.

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5) La constatation de seuil différentiel d'intensité très élevé au dessus de 3 est souvent le fait de lésions corticales mais parfois aussi de lésions du tronc cérébral.

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En principe, tous les tests vocaux doivent donner des réponses normales à l'exception des cas où il existe une HIC qui peut s'accompagner d'altérations des tests du type cortical.

Sur ces 13 observations, 8 fois les tests vocaux étaient normaux. Sur les 5 cas avec des tests paradoxalement perturbés, 2 cas seulement doivent être considérés comme ayant des réponses erronées et inexplicables, car les 3 autres cas s'accompagnaient d'HIC (il s'agissait d'altération de la VI).

3) Épilepsies — 8 cas dont 3 épilepsies temporales

En principe, les tests vocaux doivent être normaux en dehors des épilepsies temporales où les tests du type cortical sont altérés.

Les faits sont confirmés dans 2 épilepsies temporales (altération d'ailleurs bilatérale des tests corticaux); dans 4 épilepsies non temporales, tous les tests sont normaux.

Par contre, dans deux observations, les réponses des tests étaient erronées par rapport au diagnostic clinique : 1 épilepsie temporale avec altération de la VI ; 1 épilepsie non temporale (petit mal) où seule la VI était altérée.

4) Lésions du tronc cérébral — 6 cas

En principe, seuls les tests du type central et spécialement la VAI doivent être altérés, avec les restrictions habituelles en cas d'HIC pour les tests corticaux.

Sur ces 6 observations, 3 cas répondent parfaitement à ce schéma ; 3 cas donnent des réponses non concordantes avec ce schéma, dont 2 cas de syndrome d'origine traumatique (les tests tonals étaient également normaux), mais en fait dans un seul cas (gliome) les tests vocaux avaient donné des réponses erronées puisque normales.

Valeur sémiologique des tests tonals et vocaux

Les résultats obtenus dans ces 48 observations viennent confirmer la valeur sémiologique de ces différents tests. En effet, le nombre de réponses franchement erronées est de 6 pour le TRA, de 3 pour la VIB et de 11 cas pour l'ensemble des cas vocaux.

Il est possible d'apporter quelques précisions sur la valeur sémiologique de ces tests, en tenant compte et des travaux antérieurs et des résultats obtenus dans les observations objets de ce travail.

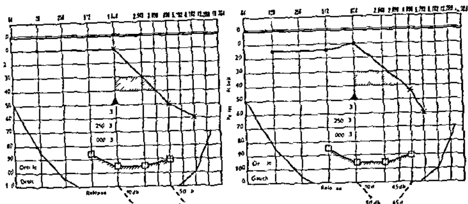


Fig 4

TRA 150		TRC 200	TRA = 150	
Vocale s n ple	100 %		Vocal simple	100 %
Voix interrompue	10 %		Voix interrompue	10 %
Voix filtr e	80 %		Voix filtree	"0 %
Vo x acceler e	100 %		Voix accél ree	10) %
Voix alternee 6 à 8 IS	0 %		Voix alternee 6 à 8 IS	0 %

1) *Le TRA* lorsqu il est altere traduit une lesion des aires auditives La prolongation est soit unilaterale géneralement homolaterale soit bilateral Il est donc difficile d apres ce test de preciser le cote de la lesion

A cette règle generale un TRA prolonge traduit une lesion temporale il convient d apporter certaines restrictions Les TRA sont generalement prolonges pour les 2 oreilles en cas HIC et parfois dans les atrophies cerebrales Les TRA sont toujours tres prolonges en cas de presbyacousie L alteration de ce test necessite des lesions neurologiques relativement importantes puisque les TRA sont normaux dans les epilepsies temporales

2) *Le test d integration bi auriculaire* Les reponses pathologiques s observent dans les lesions centrales soit sous cortical soit du tronc cerebral

Par ce test il n est pas possible de distinguer entre lesion sous corticale et lesion du tronc cerebral On pourrait penser qu une lesion du tronc cerebral donne des troubles bilateraux du TIB tandis qu une lesion sous corticale donne un trouble unilateral de ce test L experience montre qu il *n en est rien* La seule precision que l on puisse apporter est qu un trouble unilateral de ce test est en regle homolaterale a la lesion Ce caractere homolateral *n est qu* apparent car dans le TIB le facteur actif est en fait le son controlateral le SAI de l oreille homolaterale n ayant qu un role passif

3) *Le test du controle central de la fatigue* a rappelons le la meme valeur que le TIB aussi n est il recherche qu exceptionnellement

4) *Le Relapse du type II* est tres frequent dans les lesions du tronc cerebral

5) La constatation de seuil differentiel d intensite très eleve au dessus de 3 est souvent le fait de lesions corticales mais parfois aussi de lesions

Tests vocaux

Seuls les troubles unilatéraux doivent être pris en considération En effet, les altérations bilatérales et symétriques sont d'interprétation difficile Sans doute de telles altérations comme la justement remarqué Bocca, peut être le fait de lésions sous-corticales, mais elles peuvent aussi traduire des troubles aphasiques connus ou méconnus cliniquement Elles peuvent relever d'un certain déficit psychique ou de l'inattention du sujet A l'inverse des réponses paradoxalement normales, étant donné le siège de la lésion, ont été observées chez des sujets jeunes, intelligents, aptes psychologiquement sans doute, grâce à un effort d'attention, et à des phénomènes de suppléance mentale à surmonter les difficultés d'intelligibilité présentées par ces tests Un autre élément peut intervenir, c'est l'entraînement Des sujets peuvent au premier examen présenter des troubles de l'intelligibilité à ces tests, et donner par la suite des réponses normales

Les tests corticaux

Il convient de souligner, après Bocca, que ces tests peuvent être perturbés *bilatéralement en cas d'hypertension intra-crânienne*

Le test de la voix filtrée est un test plus valable que le test de la VA, car plus souvent altéré L'altération est en règle controlatérale, mais parfois homolatérale ou même bilatérale

Il est à noter que ce test ne peut être recherché lorsqu'on se trouve en présence d'un déficit tonal important ou d'une baisse limitée aux fréquences aiguës

La voix accélérée Son altération est généralement controlatérale Ce test a une valeur moins constante, il semble exiger des lésions centrales plus étendues Il semblerait qu'on puisse, théoriquement, faire un rapprochement entre ce test et le TRA Le rapprochement est souvent noté, mais non toujours De plus l'altération du TRA est généralement homolatérale celle de la VA est le plus souvent controlatérale

Tests centraux

Pour la voix interrompue comme l'a déjà souligné Bocca, l'altération est généralement controlatérale dans les lésions souscorticales, bilatérales ou homolatérales dans les lésions du tronc cérébral cependant cette règle ne nous semble pas absolue

Pour la voix alternée, les altérations semblent plus fréquentes dans les lésions du tronc cérébral

Pour schématiser la valeur séméiologique de ces tests tonals et vocaux nous donnerons 4 observations types

1) *Observation de lésion corticale superficielle Fig 1* Méningiome temporal droit Seuls les tests du type cortical sont altérés Prolongation bilatérale du TRA mais à prédominance homolatérale, altération controlatérale de la VA et de la VF Par contre intégrité de tous les tests du type central (TIB–VI–VAT)

2) *Observation de lesion corticale a extension profonde* Fig 2 Gliome temporal gauche Dans ce cas non seulement les tests du type cortical sont alteres — TRA bilateral a predominance controlaterale, VA–VF bilaterale à predominance controlatérale —, mais également les tests du type central TIB bilatéral, VI La VAT est normale mais ce test interroge surtout les voies auditives inferieures A noter ici une elevation considerable du SDI (4 et 5)

3) *Observation sous corticale temporale* Fig 3 Hematome intra-temporal gauche Seule les tests du type central (TIB VI) sont alteres On ne peut tenir compte ici des troubles de la VF étant donne la coexistence d une atteinte cochleaire

4) *Observation de lesion du tronc cerebral* Fig 4 Gliome du tronc cerebral Les tests corticaux sont normaux (TRA–VA) Pour la VF elle est ici sans valeur du fait de l'atteinte cochleaire Par contre, tous les tests centraux sont altérés A noter l existence d un Relapse du type II (deterioration du seuil tonal de 60 db à droite, 40 db a gauche pour la frequence 1000) de plus existence d un SAI eleve a 3

CONCLUSIONS

L etude critique de ces resultats obtenus dans ces 48 observations par l tests tonals et par les tests vocaux ont confirme les conclusions anterieur sur la valeur semiologique de ces tests Dans la majorite des cas il y concordance entre les conclusions tirees de ces deux tests et le diagnost neurologique Sans doute existe t il des cas exceptionnels de discordan avec la clinique (1 seul cas sur 48) et des cas rares ou les reponses d tests tonals et vocaux ne sont pas entièrement concordants Mais dans grande majorité des cas ont peut dire que par ces tests ont dispose d u methode d investigation valable pour l etude des troubles auditifs, cortica ou centraux

SUMMARY

In 48 neurologic observations tonal and vocal tests of cortical and cent deafness have been studied The results obtained have been compared w the previous conclusions on their respective semiologic values A critical stu of these results has corroborated the clinical importance of these two types tests

As to the tests of tonal type the time of auditive reaction, when lastin certain time correctly shows a cortical lesion, the bi auricular integration t when perturbed shows a sub cortical lesion or else a lesion of the cereb trunk Very high differential intensity thresholds can be seen in cortical lesi and also in those of the cerebral trunk

As for the vocal tests we can in agreement with Bocca differentiate betw cortical tests filtered voice accelerated voice, and cerebral tests interrup voice alternated voice

ests give concordant results Discordant ca

Tests vocaux

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Les tests corticaux

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Le test de la voix filtrée est un test plus valable que le test de la VA, car plus souvent altéré L'altération est en règle controlatérale, mais parfois homolatérale ou même bilatérale

Il est à noter que ce test ne peut être recherché lorsqu'on se trouve en présence d'un déficit tonal important ou d'une baisse limitée aux fréquences aigues

La voix accélérée Son altération est généralement controlatérale Ce test a une valeur moins constante, il semble exiger des lésions centrales plus étendues Il semblerait qu'on puisse, théoriquement, faire un rapprochement entre ce test et le TRA Le rapprochement est souvent noté, mais non toujours De plus l'altération du TRA est généralement homolatérale, celle de la VA est le plus souvent controlatérale

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Pour la voix interrompue comme l'a déjà souligné Bocca, l'altération est généralement controlatérale dans les lésions souscorticales, bilatérales ou homolatérales dans les lésions du tronc cérébral, cependant cette règle ne nous semble pas absolue

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Pour schématiser la valeur sémiologique de ces tests tonals et vocaux, nous donnerons 4 observations types

1) *Observation de lésion corticale superficielle Fig 1* Méningiome temporal droit Seuls les tests du type cortical sont altérés Prolongation bilatérale du TRA mais à prédominance homolatérale, altération controlatérale de la VA et de la VF Par contre intégrité de tous les tests du type central (TIB-VI-VAT)

ASPIRATION BIOPSY OF SALIVARY GLAND TUMOURS

I. Correlation of Cytologic Reports from 652 Aspiration Biopsies with Clinical and Histologic Findings

P. Mavec[1,2], C. M. Eneroth[3], S. Franzén[4], G. Moberger[5] and J. Zajicek[2]

Stockholm, Sweden

From Cytology Department of Radiumhemmet,[2] the Department of Otolaryngology,[3] the General Department of Radiumhemmet[4] and the Institute of Radiopathology,[5] Karolinska Sjukhuset, Stockholm

Critical analysis of cytologic reports from aspiration biopsy of salivary glands in 652 cases showed that positive diagnosis had been made in 92 per cent of the cases with tumour. In 8 per cent of cases the cytologic method can be expected to give false negative reports concerning tumour. The possibility of false positive tumour diagnosis can be disregarded, however, if the cytologist is fully familiar with the morphology of salivary gland cells in various pathologic conditions. Recognition of the malignancy of salivary gland tumours by cytologic technique is discussed and also the possible risk of local or distant spread of tumour following aspiration biopsy.

An impressive volume of literature bears testimony to the value of aspiration biopsy for diagnosis of tumours in various organs (Berg 1961, Cardozo 1954, Martin & Ellis 1930), especially breast (Bonneau, Sommer & De The, 1960, Cornillot & Verhaeghe, 1955, Marsan & Bertini 1960, Zajdela 1963, Zajicek 1963), prostate (Esposti & Zajicek 1963, Franzén, Giertz & Zajicek 1960), thyroid gland (Einhorn & Franzén 1962) and lung (Grunze 1960). As yet, however, no detailed evaluation of aspiration biopsy in tumours of the salivary glands has been reported.

At Radiumhemmet aspiration biopsy is extensively used and for many years it has been performed in suspected salivary gland tumours in order to obtain cytologic information *prior to radiotherapy or surgical treatment.* In our experience cytologic diagnosis of salivary gland tumours is extremely difficult, partly because of the great diversity of tumour types and partly because of the heterogeneity of cell populations in individual tumours. A detailed morphologic study of cell populations from suspected salivary gland tumours as found on smears of aspirate and correlation of cytologic findings with histologic diagnosis seemed therefore to be highly warrantable.

With these aims in mind, we have reviewed the aspiration biopsies made

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ZUSAMMENFASSUNG

In 18 Beobachtungen wurden die tonalen und vokalen Tests für Rinden und zentrale Gehörschädigungen untersucht. Die Ergebnisse wurden mit den vorherigen Schlussfolgerungen auf ihren semiologischen Wert hin verglichen. Die kritische Untersuchung dieser Ergebnisse hat die klinische Brauchbarkeit dieser beiden Test-Typen bestätigt.

Was die Tests vom tonalen Typ anbelangt, so zeigt eine Verlängerung der Zeit der Gehörsreaktion eine Rindenschädigung an; der Test der Integrierung durch *beide Ohren* zeigt, wenn er gestört ist, eine subkortikal Schädigung oder eine Schädigung des Hirnstamms an. Der Relapsus des Typs II lässt auf eine Hirnstammschädigung schliessen. Eine schmerzhaft erhöhte Hörschwelle finden wir bei Rinden- sowie bei Hirnstammschädigungen.

Was die Stimmtests anbelangt, kann man mit Bocca zwischen Rindentests gefilterter Stimme und beschleunigter Stimme unterscheiden, sowie bei Gehirntests zwischen unterbrochener und alternierender Stimme.

Insgesamt ergeben tonale und Stimmtests übereinstimmende Resultate; das Gegenteil ist nur in Ausnahmefällen festzustellen.

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Fig 1 Aspiration biopsy of a case with a mixed tumour in left parotis One hand grip of the syringe while biopsy is made is shown The plunger of the syringe is retracted during aspiration

stained with the May–Grunwald Giemsa stain commonly used in haematology In some cases of the present series especially when the aspirate was rich in cells these slides were supplemented by smears fixed before drying in 0 per cent ether ethylalcohol mixture and stained according to Papanicolaou

Cytologic diagnosis

In most of the cases the aspiration biopsy and the cytologic diagnosis were made by the same persons (Franzen or Zajicek) The cytologic observations presented in the tables were made at the time of aspiration biopsy Revised diagnostic opinions arising from review of the material are discussed in the text

Histologic classification

In the first years of the study tumours of the salivary glands were classified at
son (192
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at Radiumhemmet on salivary glands. The present paper concerns correlation of cytologic findings with clinical and histologic diagnosis, and hence the usefulness and limitations of such cytologic aspiration biopsy in the diagnosis of salivary gland tumours. The review of the morphologic appearance of tumour cells in smears prepared from aspirate will be reported later.

MATERIAL AND METHODS

During the period 1953 through 1962, aspiration biopsy of salivary glands was performed at Radiumhemmet in 652 cases. In 177 cases (*series A*) the biopsy was not followed by surgical treatment, and therefore the cytologic observations could be correlated only with the clinical findings. In the other 475 cases (*series B*) operation was performed after aspiration biopsy, and consequently histologic findings were available for comparison.

Technique of aspiration biopsy

The apparatus consists of an ordinary 22 gauge needle attached to a 10 ml Record syringe of Luer-Lok type. The syringe has a special handle which allows a one-hand grip while biopsy is being made (Franzen, Giertz & Zajicek, 1960). Use of the thin needle minimizes admixture of blood. Occasionally, however, a thicker needle may have to be substituted, if the initial puncture suggests presence of fibrotic tissue.

The skin of the site is wiped with an antiseptic and the suspected tumour is held with one hand in a position favourable for needle biopsy. When the needle has entered the tumour area the plunger of the syringe is drawn back as far as possible, thus creating a vacuum in the system, and meanwhile the needle proceeds in a straight line through the lesion. In this way material is aspirated into the needle. In order to obtain sufficient material, particularly from fibrotic lesions, the needle may have to be moved back and forth four to five times, and possibly inserted into different areas. Throughout this manipulation, negative pressure is maintained by retracting the plunger of the syringe (Fig. 1).

When the aspiration has been completed the pressure in the syringe is allowed to equalize and the needle is then withdrawn from the tumour. The syringe is disconnected from the needle, filled with air and reconnected. The material in the needle is carefully expressed onto a glass slide. If the aspirate is haemorrhagic, or if it contains a fairly large volume of tissue fluid, it must be spread on the slide with the aid of a thick coverslip (such as that used in a Burker counting chamber) as for an ordinary blood smear. Relatively large tissue fragments that collect at the end of the smear are gently squeezed by firm flat pressure with the coverslip previously used to spread the smear. If the aspirate is highly cellular and without admixture of blood, it is spread along the slide by flat pressure with the coverslip. The smears are dried in air at room temperature, after which they are



Fig 1 Aspiration biopsy of a case with a mixed tumour in left parotis One hand grip of the syringe, while biopsy is made is shown The plunger of the syringe is retracted during aspiration

stained with the May–Grünwald Giemsa stain commonly used in haematology In some cases of the present series, especially when the aspirate was rich in cells, these slides were supplemented by smears fixed before drying in 50 per cent ether–ethylalcohol mixture and stained according to Papanicolaou

Cytologic diagnosis

In most of the cases the aspiration biopsy and the cytologic diagnosis were made by the same persons (Franzén or Zajicek) The cytologic observations presented in the tables were made at the time of aspiration biopsy Revised diagnostic opinions arising from review of the material are discussed in the text

Histologic classification

In the first years of the study, tumours of the salivary glands were classified at [illegible] son (1924 [illegible] however, [illegible] recently the scheme recommended by Foote & Frazell (1954) was adopted for routine use The histologic slides were therefore reviewed in all cases and, if necessary, the tumours were reclassified according to the latter nomenclature

RESULTS

Series A: Aspiration Biopsy Findings in 177 Cases without Histologic Diagnosis

Table 1 presents some clinical information on the cases in which aspiration biopsy was not followed by surgery.

Columns 1 and 2 show that in 101 cases the clinical picture did not suggest salivary gland tumour. In 24 of these cases, however, the clinical observations made follow-up advisable The most common cytologic findings in this group were normal salivary gland cells (cf. Figs 2 *a*, *b*, *c*) with or without inflammatory cells and cystic contents, which in 12 of 15 cases consisted of saliva-like fluid containing no cells

In 12 cases aspiration biopsy was performed because of slight clinical suspicion of recurrence of previously excised mixed salivary gland tumour The cytologic examination revealed no tumour cells and, as the clinical picture normalized, no operation was performed; continued follow-up was recommended In 7 of the 12 cases the cytologic examination showed inflammatory cells, mainly granulocytes, histiocytes and foreign-body giant cells.

In 22 cases metastasization to the salivary glands of distant primary carcinoma was clinically suspected, but in no case did the aspiration biopsy demonstrate malignant cells The site of the primary carcinoma was the tongue (9 cases), nasopharynx (4 cases), lips (2 cases), thyroid (2 cases), larynx (1 case), or lungs (2 cases) In 2 cases the site of the primary tumour was unknown, but there was general skeletal metastasization In 17 of the 22 cases only normal salivary gland cells were found by aspiration biopsy

In 9 cases the clinical observations and the finding of benign tumour cells or cystic contents in aspiration biopsy specimens made operation advisable Three of the patients declined surgical treatment, however, and in 6 cases such treatment was precluded by poor general condition

Finally, there were 33 cases in which malignant cells were demonstrated by aspiration biopsy, but which were clinically considered to be inoperable and were therefore referred for radiotherapy This group included 7 cases of malignant lymphoma and 22 cases of carcinoma in which operation was precluded by the patient s high age (3 cases), extensive local infiltration of the tumour (10 cases), or because the salivary tumour apparently was metastatic from the nasopharynx (3 cases), skin (2 cases) larynx (1 case), or breast (3 cases) There were also 4 cases of recurrence of malignant salivary gland tumour in which surgery was contraindicated by extensive local infiltration (2 cases) or high patient age (2 cases)

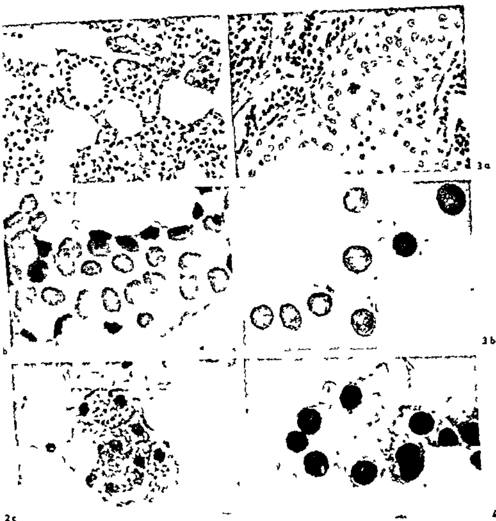


Fig 2 (*a*) Section of a parotid gland showing serous terminal portions and a duct, numerous fat cells haematoxylin eosin stain ×160 (*b*) A cluster of ductal epithelial cells in aspirate (smear) Giemsa stain ×400 (*c*) Serous epithelium in aspirate (smear), Giemsa stain ×240

Fig 3 (*a*) Section of papillary adenolymphoma with abundant lymphoid tissue in stroma haematoxylin eosin stain ×160 (*b*) Epithelial cells (oncocytes) in aspirate from a papillary adenolymphoma (smear), Giemsa stain ×400

Fig 4 Aspirate from acinic cell carcinoma (smear) Giemsa stain ×400

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In 9 cases the clinical observations and the finding of benign tumour cells or cystic contents in aspiration biopsy specimens made operation advisable. Three of the patients declined surgical treatment, however, and in 6 cases such treatment was precluded by poor general condition.

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TABLE 1 *Clinical and cytologic (aspiration biopsy) findings in cases of salivary gland lesion without surgical treatment*

	Clinical findings						
	No tumour						
Cytologic findings	no follow up required	follow up advised	Suspected recurrence of tumour	Suspected metastasis	Tumour[a]	Inoperable tumour	Total
Blood only			2				2
Salivary gland cells	27	7	3	17			54
Salivary gland cells + inflammatory cells	12	6		4			22
Inflammatory cells	7	2	7				16
Lymphocytes	18	7		1			26
Cystic contents	13	2			1		16
Benign tumour cells					8		8
Malignant lymphoma						7	7
Carcinoma						22	22
Recurrence of tumour						4	4
Total	77	24	12	22	9	33	177

[a] Operation unfeasible or refused

Series B Aspiration Biopsy Findings in 475 Cases with Histologic Diagnosis

Table 2 shows the site of the lesions and the histologic diagnoses in the 475 cases in which histologic and cytologic findings could be compared. In 42 cases no tumour was found in the surgically excised tissue. Histologic examination showed benign tumour tissue in 309 cases and malignant tumour in 124 cases, 35 of the benign tumours and 33 of the malignant growths being local recurrences.

TABLE 2 *Site and histologic diagnosis of salivary gland lesions previously cytologically studied (by aspiration biopsy)*

Site of lesion	No tumour	Primary tumour: benign tumour	Primary tumour: malignant tumour	Recurrent tumour: benign tumour	Recurrent tumour: malignant tumour	Total
Parotid gland	33	262	73	31	26	425
Submandibular gland	9	11	14	4	5	43
Minor salivary glands			4		2	6
Sublingual gland		1				1
Total	42	274	91[a]	35	33	475

[a] [illegible] ...ted malignancy

TABLE 4 *Cytologic findings in cases histologically classified as benign salivary gland tumours*

Cytologic findings	Histologic findings				Total
	Cystadeno lymphoma	Benign mesenchymal tumour	Onco-cytoma	Benign mixed tumour	
No cells in specimen		1		1	2
Normal salivary gland cells	2			1	3
Cystic contents	11	1		4	16
Inflammatory cells, cell detritus	4				4
Tumour cells classification not possible	1			8	9
Cystadenolymphoma	8				8
Oncocytoma	5		3		8
Suspected mixed tumour				11	11
Mixed tumour benign[a]	1			204	205
Mesenchymal tumour		5			5
Carcinoma	1			2	3
Total	33	7	3	231	274

[a] In 10 cases malignancy was suspected

ever is that between aspiration biopsy of the parotid and removal of that gland the patient received intensive local irradiation (5000 r), which could have explained the negative histologic result

Histologically benign salivary gland tumours

The cytologic findings in the 274 cases in which a primary operation revealed benign salivary gland tumour are presented in Table 4

In the 33 cases of cystadenolymphoma the diversity of the cytologic findings demonstrates the difficulty of diagnosing this tumour by means of aspiration biopsy In only 8 of the 33 cases did the cytologic examination clearly show cystadenolymphoma In 11 cases the aspirate consisted solely of cystic contents, usually fluid with admixture of inflammatory cells In 4 cases inflammatory cells and cell detritus were the main characteristics of the aspirate A cytologic diagnosis of oncocytoma was made in 5 cases of cystadenolymphoma, because of abundant "oncocytes" (Hamperl, 1962) on the smears On Giemsa stained smears oncocytes appeared as epithelial cells with rich cytoplasm and a round, often excentrically sited nucleus (cf Figs 5a b) Review of the cytologic slides revealed oncocytes in 22 of the 33 cases of cystadenolymphoma and our present experience suggests that presence of these cells in aspirate is indicative of cystadenolymphoma One of the histologically diagnosed cystadenolymphomas was cytologically classified as carcinoma Aspiration biopsy had yielded a large amount of necrotic material containing groups of degenerated cells, and on Giemsa-

TABLE 3. *Cytologic findings in cases of salivary gland lesion with tumour negative histologic report*

Cytologic findings	Histologic findings							
	Sialadenitis	Nonspecific lymphadenitis	Tuberculous lymphadenitis	Abscess	Foreign-body granuloma	Lymphoepithelial lesion	Cyst	Total
No cells in specimen				1		1	1	3
Salivary gland cells	7	1	1					9
Cystic contents	1					2	6	9
Inflammatory cells	6		2	1	6			15
Lymphocytes		1	1			2		4
Benign tumour cells	1							1
Malignant tumour cells	1							1
Total	16	2	4	2	6	5	7	42

In 425 (89,5 per cent) of 475 surgically treated cases the parotid region was involved. The lesion occurred in submandibular gland in 43 cases, in minor salivary glands in 6 cases and in sublingual gland in 1 case.

The cytologic findings from aspiration biopsy in these 475 cases are presented in Tables 3 to 6.

Histologically tumour-negative cases

Table 3 shows the cytologic findings in the 42 cases in which histologic examination revealed no tumour of the salivary glands. The histologic diagnoses in these cases were sialadenitis (16 cases), nonspecific lymphadenitis (2 cases), tuberculous lymphadenitis (4 cases), abscess (2 cases), foreign body granuloma (6 cases), lymphoepithelial lesion (5 cases) and congenital or retention cyst (7 cases).

It is seen that the cytologic reports were largely in conformity with these diagnoses. In one case, however, the cytologist reported benign tumour, whereas the histologic examination showed nonspecific sialadenitis. Review of the cytologic slides showed that degenerated ductal epithelial cells had been mistakenly interpreted as benign tumour cells. This "false positive" report could be attributed to lack of experience in the special field of cytology and could have been avoided by more expert scrutiny.

In another case the cytologist reported malignant tumour cells, but the histologist found only nonspecific sialadenitis. The patient had primary carcinoma of the breast and the clinical picture suggested spread to the parotid region. Review of the cytologic slides and comparison with slides made from aspiration biopsy of the mammary tumour showed that the presumed carcinoma cells in the parotid region had the same morphologic characteristics as those aspirated from the breast. A relevant point, how-

TABLE 4. *Cytologic findings in cases histologically classified as benign salivary gland tumours*

	Histologic findings				
Cytologic findings	Cystadeno-lymphoma	Benign mesenchymal tumour	Onco-cytoma	Benign mixed tumour	Total
No cells in specimen		1		1	2
Normal salivary gland cells	2			1	3
Cystic contents	11	1		4	16
Inflammatory cells, cell detritus	4				4
Tumour cells, classification not possible	1			8	9
Cystadenolymphoma	8				8
Oncocytoma	5		3		8
Suspected mixed tumour				11	11
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In the 33 cases of cystadenolymphoma the diversity of the cytologic findings demonstrates the difficulty of diagnosing this tumour by means of aspiration biopsy. In only 8 of the 33 cases did the cytologic examination clearly show cystadenolymphoma. In 11 cases the aspirate consisted solely of cystic contents, usually fluid with admixture of inflammatory cells. In 4 cases inflammatory cells and cell detritus were the main characteristics of the aspirate. A cytologic diagnosis of oncocytoma was made in 5 cases of cystadenolymphoma because of abundant oncocytes (Hamperl 1962) in the smears. On Giemsa stained smears oncocytes appeared as epithelial cells with rich cytoplasm and a round, often eccentrically sited nucleus (cf. Figs. 7a, b). Review of the cytologic slides revealed oncocytes in 22 of the 33 cases of cystadenolymphoma and our present experience suggests that presence of these cells in aspirate is indicative of cystadenolymphoma. One of the histologically diagnosed cystadenolymphomas was cytologically classified as carcinoma. Aspiration biopsy had yielded a large amount of necrotic material containing groups of degenerated cells, and on Giemsa

TABLE 3. *Cytologic findings in cases of salivary gland lesion with tumour-negative histologic report*

Cytologic findings	Histologic findings: Sialadenitis	Nonspecific lymphadenitis	Tuberculous lymphadenitis	Abscess	Foreign body granuloma	Lymphoepithelial lesion	Cyst	Total
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Salivary gland cells	7	1	1					9
Cystic contents	1					2	6	9
Inflammatory cells	6		2	1	6			15
Lymphocytes		1	1			2		4
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the cytologic slides In 11 other cases the cytologic examination suggested mixed tumour Cytologic diagnosis of benign mixed salivary gland tumour was made from aspiration biopsy in 204 cases but in 10 of them pronounced cell atypia suggested malignancy Two cases which histologically were classified as benign mixed tumour were cytologically described as carcinoma One of these patients died of carcinoma with pulmonary metastases a year after the operation on the salivary gland region It is relevant however that both of the patients received preoperative irradiation (2000 and 4000 r skin dose respectively) which might have explained the discrepancy between the cytologic and histologic reports

Histologically malignant salivary gland tumours

Table 5 presents the cytologic observations in the 91 cases in which the histologic diagnosis after primary operation was malignant tumour (In 4 of the 18 cases of mixed tumour however malignancy was only suspected) In addition to the 18 mixed tumours there were 55 cases of primary salivary gland carcinoma (11 mucoepidermoid 16 adenocystic 18 acinic cell 4 adenopapillary and 6 solid anaplastic carcinomas)

In 14 of the 18 cases histologically identified as malignant or suspectedly malignant mixed tumours the cytologic report was benign mixed tumour Of the 4 cases in which malignancy was recognized or suspected at cytologic examination 3 were then described as carcinoma and the other as suspected carcinoma

In 6 of the 11 cases of histologically verified mucoepidermoid carcinoma aspiration biopsy yielded only cystic fluid Operation was performed because the swelling did not subside after aspiration In 3 of the remaining 5 cases in this group the cytologic diagnosis was carcinoma

Table 5 illustrates the difficulties that were encountered in identifying adenocystic acinic cell and adenopapillary carcinoma from smears of aspirate Only in 9 of 38 cases was malignancy diagnosed by cytologic examination In 17 cases the cytologic diagnosis was benign mixed tumour In anaplastic carcinoma by contrast 4 of the 6 histologically verified tumours were cytologically identified as carcinoma and another was suspected to be malignant

All of the 13 cases of metastatic carcinoma were correctly diagnosed by preoperative aspiration biopsy In 7 of the 13 cases there was metastatic growth of primary salivary gland carcinoma into lymphnodes close to salivary glands In the other cases metastasis of distant carcinoma had occurred to salivary gland regions (malignant melanoma in 1 case squamous cell carcinoma of the skin in 2 cases and 1 case each of carcinoma of the tongue hypopharynx and tonsils)

Of the 5 mesenchymal tumours 2 were malignant lymphomas (reticulum cell sarcoma and lymphogranulomatosis maligna) and 3 were malignant neurofibromas The reticulum cell sarcoma was identified by aspiration biopsy and the lymphogranulomatosis maligna was suspected at cytologic

TABLE 5 *Cytologic findings in cases histologically classified as malignant or suspectedly malignant salivary-gland tumours*

Cytologic findings	Histologic findings: Malignant mixed tumour	Mucoepidermoid carcinoma	Adenocystic carcinoma	Acinic cell carcinoma	Adenopapillary carcinoma	Anaplastic carcinoma	Metastatic carcinoma	Malignant mesenchymal tumour	Total
Cystic contents		6	1						7
Suspected mixed tumour	1	1		2					4
Mixed tumour, benign	13	1	10	5	2				31
Epithelial tumour, malignancy not defined			2	3	1	1			7
Epithelial tumour, suspectedly malignant	1			2	1	1			5
Carcinoma	3	3	3	6		4	13		32
Mesenchymal tumour								5	5
Total	18[a]	11	16	18	4	6	13	5	91

[a] In 4 cases only suspected malignancy

stained slides these displayed morphologic characteristics of squamous cells with nuclear atypia, which cytologically were misinterpreted as highly differentiated squamous carcinoma

The histologic examination revealed benign mesenchymal tumour in 7 cases In one of these cases (lymphangioma) the aspiration biopsy specimen contained no cells In another case (myxolipoma) the aspirate consisted of an abundant amorphous mass which cytologically suggested cystic contents In 5 cases (4 neurofibromas and 1 lipoma) the derivation of the tumour was correctly recognized from *cytologic smears although* in 2 of the tumours with neurofibromatous structure extreme polymorphism then suggested sarcoma Both of these latter patients received heavy preoperative *irradiation (5000 r) Because of extensive degenerative changes* in the tumours following radiotherapy, the question of malignancy could not be conclusively answered from the surgically removed specimens

Three cases of oncocytoma were correctly diagnosed by aspiration biopsy In all 3 cases the aspirate contained abundant 'oncocytes' which in 2 cases were morphologically similar to the oncocytes found in cases of cystadeno lymphoma In the third case the cells were larger and showed nuclear atypia, and mitotic figures were not uncommon

The histologic diagnosis was benign mixed tumour in 231 cases Aspiration biopsy yielded no tumour cells in 6 of these cases In 8 cases tumour was diagnosed from the aspirate, but classification could not be made from

in only 5 of 11 tumours of this type were suitable cells obtained for cytologic diagnosis. In the other 6 cases the aspirate consisted solely of cystic fluid. Consequently, a report of cystic fluid from aspiration biopsy should not be accepted as a final diagnosis. Removal of cystic fluid from a tumour, however, permitted re-evaluation of the clinical observations. When a swelling subsided completely after biopsy and other palpatory findings normalized, patients could as a rule be freed from follow-up. But if palpation after aspiration of cystic fluid evoked any suspicion of a persistent lesion, surgery was undertaken.

As regards the possibility of "false positive" tumour diagnosis from aspiration biopsy, the reader is referred to Table 3. In one case in this table the histologic diagnosis was sialadenitis, whereas the cytologic report from *aspiration biopsy was benign tumour*. The cytologic error was attributable to inadequate knowledge of the morphologic appearance of chronically inflamed salivary gland epithelium in an early period of this study (1956), and it could therefore have been avoided by more competent *analysis*. *In* another case the cytologic examination indicated metastasis of mammary carcinoma to the parotid region. Although the *subsequently* made histologic examination revealed no parotid malignancy, we do not regard the cytologic report as false positive, since review of all the material *in the case* made it apparent that heavy *preoperative irradiation (5000 r)* could be considered responsible for disappearance of tumour cells from that *region*.

Our study thus indicated that cytologic examination of material obtained by aspiration biopsy from salivary glands *may yield a false negative* diagnosis of tumour in about 8 per cent of cases. The *possibility of false positive* diagnosis, on the other hand, can be disregarded *if the cytologist is* fully conversant with the morphologic appearance of salivary gland cells *in smears made* from various pathologic lesions.

In order to decide if a tumour should be treated by surgery (e.g. mixed tumours) *or radiotherapy* (e.g. malignant lymphoma or metastatic carcinoma), *how radical an operation* should be, and whether or not preoperative radiotherapy is *advisable*, the clinician requires, in addition to simple confirmation of tumour *presence*, *information* on its structural type and particularly on *its possible* malignancy. We must therefore consider how frequently aspiration biopsy yields such information as compared with histologic examination.

Table 4 shows that among 274 cases histologically regarded as benign tumours (cystadenolymphoma, *oncocytoma*, benign mesenchymal or mixed tumour) the same *diagnosis had been* made by cytologic examination in 220 cases (80.3 per cent) comprising 8 *cystadeno*lymphomas, 5 mesenchymal tumours, 3 oncocytomas and 204 mixed tumours. (In 10 of the benign mixed tumours, however, *malignancy* was suspected at cytologic examination.)

In 54 cases the cytologic diagnosis differed from the *histologic report*

TABLE 6. *Cytologic findings in cases with histologically verified recurrence of salivary gland tumours.*

Cytologic findings	Histologic findings: Recurrence of benign tumour	Recurrence of malignant tumour	Total
No tumour cells	4		4
Suspected recurrence	4	3	7
Recurrence	27	30	57
Total	35	33	68

examination. The histologically diagnosed malignant neurofibromas were cytologically recognized as mesenchymal tumours, but malignancy was not discussed in the reports.

Histologically recurrent salivary gland tumours

The cytologic and histologic findings in 68 cases in which operation was performed because of suspected recurrence of salivary gland tumour are shown in Table 6. Four "false negative" cytologic reports were given in cases of benign recurrent tumour, *but there was no false negative cytologic result* in the 33 histologically malignant recurrent tumours.

DISCUSSION

In discussing the value of aspiration biopsy for the therapeutic management of salivary gland tumours, one must primarily consider what information the clinician seeks from the biopsy. In our opinion, the points to be elucidated before treatment is begun are as follows. Is the lesion a tumour? Is surgery or radiotherapy indicated? How radical should an operation be? Is preoperative radiotherapy advisable?

Evaluation of the potentialities of aspiration biopsy to provide answers to these questions is possible only by comparing the cytologic reports with subsequent histopathologic findings in the same cases. Such comparisons could be made in the 475 cases comprising series B in our clinical material.

With regard to recognition of tumour, Tables 1 to 6 show that in 375 of 433 histologically diagnosed salivary gland tumours a cytologic report of tumour had already been made from aspiration biopsy and in 22 more cases tumour had been cytologically suspected. This amounts to 92 per cent preoperative recognition of tumour. In the remaining 8 per cent of the series aspiration biopsy gave a "false negative" result. Most commonly this was because the aspirate contained *no cells, and as a rule in these cases* the tumour was partly cystic (cf. Tables 4 and 5).

False negative cytologic reports due to aspiration of cystic fluid were very frequent *in cases of mucoepidermoid carcinoma*. Table 5 shows that

in only 5 of 11 tumours of this type were suitable cells obtained for cytologic diagnosis In the other 6 cases the aspirate consisted solely of cystic fluid Consequently, a report of cystic fluid from aspiration biopsy should not be accepted as a final diagnosis Removal of cystic fluid from a tumour however, permitted re-evaluation of the clinical observations When a swelling subsided completely after biopsy and other palpatory findings normalized patients could as a rule be freed from follow up But if palpation after aspiration of cystic fluid evoked any suspicion of a persistent lesion surgery was undertaken

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In 54 cases the cytologic diagnosis *differed from* the histologic report

The reason for the tumour-negative cytologic report in 25 cases was absence of tumour material in the aspirate. In the *remaining 29 cases the presence* of tumour was recognized but, because of insufficient knowledge of the morphology of salivary gland tumour cells in smear preparations, detailed identification of tumour type was not made. For example, in cystadenolymphoma the diagnostic significance of "oncocytes" intermingled with inflammatory cells on smears is now understood, but initially 7 cystadenolymphomas were wrongly classified as oncocytoma (5 cases), mixed tumour (1 case) or carcinoma (1 case).

It is relevant to the problem of recognizing malignancy that of 274 tumours histologically classified as *benign, only 3 had been cytologically reported* as malignant (Table 4). One was a cystadenolymphoma in which degenerated oncocytes resembled squamous epithelial cells and were thought by the cytologist to derive from metastatic, highly differentiated squamous cell carcinoma. Two other tumours cytologically diagnosed as carcinoma were histologically classified as benign mixed tumour. As mentioned, however, these two patients had received preoperative local irradiation. Review of the slides indicated that, although the cytologic diagnosis of carcinoma was wrong in the case of cystadenolymphoma, it could be regarded as *correct in the two "mixed tumours" (One of the latter patients died of* pulmonary metastases a year later.) The heavy preoperative irradiation can be considered responsible for disappearance of morphologically malignant tumour cells, and consequently for the negative histologic findings in the specimens from operation.

In tumours histologically classified as malignant, cytologic reports lacked detailed information of tumour type. Table 5 shows that among 18 cases histologically considered to be malignant mixed tumours, the malignancy was cytologically diagnosed in only three cases and was suspected in one. Similarly, in 55 cases of primary carcinoma of the salivary gland region malignancy was cytologically diagnosed or suspected in only 20 cases. These are extremely low figures.

The evident discrepancy between cytologic and histologic findings concerning detailed classification of tumours and recognition of malignancy may, however, be largely explained by *the fact that Masson's classification* was used by cytologists and histologists alike at the time when the diagnoses were made. In consequence tumours such as adenocystic or acinic cell carcinoma were previously regarded at Radiumhemmet as a variety of mixed salivary gland tumours. Since that time the *histologic* diagnosis of all the cases in Table 5 has been revised in conformity with the nomenclature suggested by Foote & Frazell (Table 5 shows the latest classification) but the revision was not extended to the cytologic diagnoses. This circumstance may explain the high frequency of cytologic diagnosis of mixed tumour as compared with the reclassified histologic reports. Review of the cytologic slides now suggests that some carcinomas, notably the acinic cell type, possess characteristic cytologic features which in future

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In summary it may be said that as regards cytologic recognition of malignancy in salivary gland tumours by means of aspiration biopsy no false positive reports of malignancy need be anticipated on condition that *the slides are read by experienced cytologists* This conclusion is based on the fact that in our series of cases *only one false positive cytologic diagnosis of malignancy was made in 274 cases of benign tumour* On the other hand considerable difficulty was experienced in recognizing malignancy as such *Of 73 primary malignant tumours only 19 were clearly recognized as malignant from cytologic smears* Further morphologic studies of tumour aspirate will doubtless improve results in this respect

Finally the question of risk to the patient from aspiration biopsy must be considered In the present series of 652 salivary gland biopsies no significant complications occurred Only occasionally did small haematomas form However two other possible untoward effects of aspiration biopsy must be taken into account The first is whether or not local spread of tumour may follow the biopsy, and the second is if the biopsy can give rise to distant metastasis thus impairing the prognosis in the individual case

The possibility of local dissemination was investigated in benign mixed tumours which because they are encapsulated, are well suited for such studies In seven cases in which aspiration biopsy had been performed serial sectioning of the excised tumour area revealed no tumour material outside the capsule (Lneroth Fluur & Zajicek 1963) Moreover, follow up of the cases of benign mixed tumour in Table 4 showed that in 89 patients with at least five years of observation there was no recurrence after surgical removal of the tumour From this it may be inferred that aspiration biopsy does not involve risk of local spread of tumour

Concerning the second possibility that aspiration biopsy may give rise to distant metastasis and thus unfavourably influence prognosis no conclusions can be formed from our investigations as the number of malignant tumours is too small and the observation periods as yet are too short The reader is therefore referred to the reports by Robbins *et al* (Robbins *et al* 1964 Berg & Robbins 1962) who stated that aspiration biopsy of mammary gland carcinoma when performed with an 18 gauge needle (much thicker than the 22 gauge needle we used) seemed to have no effect on long term survival

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The reason for the tumour-negative cytologic report in 25 cases was absence of tumour material in the aspirate. In the remaining 29 cases the presence of tumour was recognized but, because of insufficient knowledge of the morphology of salivary gland tumour cells in smear preparations, detailed identification of tumour type was not made For example, in cystadenolymphoma the diagnostic significance of "oncocytes" intermingled with inflammatory cells on smears is now understood, but initially 7 cystadenolymphomas were wrongly classified as oncocytoma (5 cases), mixed tumour (1 case) or carcinoma (1 case)

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ZUSAMMENFASSUNG

Eine kritische Analyse der zytologischen Befunde bei 652 Aspirationsbiopsien der Speicheldrüse zeigte, dass in 92% der Fälle mit Tumoren eine positive zytologische Diagnose gestellt wurde. In 8% der Fälle mit Tumoren muss man bei Anwendung der zytologischen Methode mit einer falschen negativen Diagnose rechnen. Von der Möglichkeit falscher positiver Tumordiagnosen kann man absehen, wenn der Zytologe mit der Morphologie von Speicheldrüsenzellen in verschiedenen pathologischen Zuständen vollkommen vertraut ist. Die Malignitätsgradierung von Speicheldrüsentumoren mit zytologischer Technik wird diskutiert. Weiter wird die mögliche Gefahr lokaler oder metastatischer Verbreitung des Tumors als Folge der Aspirationsbiopsie diskutiert.

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CONTRIBUTION TO DOHLMAN'S HYPOTHESIS

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From the Section of Radioactive Isotopes (Head Dr Esteban Velasco) Institute of Oncology Granada

The results of our experiments with S³⁵ on chick embryos are a contribution to Dohlman's hypothesis about the role of sulfomucopolysaccharides in the excitation of the sensorial cells of the internal ear

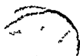
One of us (Marco & Esteban Lasala 1964) who had studied with histochemical techniques the topography of the mucopolysaccharides in the internal ear of guinea pig previously submitted to the ototoxic action of dihydrostreptomycin neomycin and kanamycin obtained results that are a contribution to Dohlman's theory We found that the quantity of mucopolysaccharides in the tectorial membrane diminished according to the degree of destruction of the Corti organ We thought that if in diminishing *the function* the mucopolysaccharides of the tectorial membrane also diminish they must have a mission, which would be possibly the *one* maintained by Dohlman

According to Dohlman's hypothesis the charge in tectorial and otolitic membrane and in the ampullaceous cupula is positive whereas in the sensorial cells it is negative The membranes covering the cilia are impermeable to ions

The changes of electric potentials in the surface of the cilia alter the sign of the sensorial cell and this change is transmitted to the nervous ends This theory is supported by Dohlman who basing himself on his experiments with S³⁵ (1960) thinks that this change of potential is determined by the sulfomucopolysaccharides produced in the secretory epithelium of the inner ear The results of his experiments add another doubt about the endolymphatic circulation which seems to be of the radial type although not exactly in the sense maintained by Naftalin and Harrison

Basing ourselves on Dohlman's experiments with S³⁵ as well as those of Belanger (1953 1956) Portmann (1954) Wislocki & Ladman (1955) with the same radioactive isotope we have begun a series of researches We tried to discover if working with this isotope we would find alterations similar to those observed with histochemical techniques or those

This paper is dedicated to Prof Marco, who aroused my interest on the problems of the internal ear



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Fig 5



Fig 6

MATERIAL AND METHODS

The eggs were placed in an incubator in standard conditions of temperature and humidity turning them around every 8–12 hours (they are turned so that the embryo does not adhere to any place) In different periods after the day when the incubation had started a little hole with a diameter of about 1 2 cm was made in the ventral portion of the egg and through it S was instilled in sulfate form ($^{35}SO_4NA_2$) in isotonic solution in a quantity of 5 microcuries The S^{35} solution was made in such a way that the above mentioned radiosulfur quantity would be contained in a drop of solution After the radiosulfur instillation, the hole of the egg was covered with a watch glass soldered with paraffin so as to avoid desiccation and again put in the incubator In order to observe the evolution of the sulfur deposition some embryos were extracted 12 hours and others 24 hours after the injection of the radio element, putting them immediately after the extraction into a saline formol solution where they were kept during a period of time which varied according to the embryo size

After being decalcified they were included in paraffin and seriated sections were made One of them was stained following the usual technique, an autoradiography was taken from another and in another two the histo



Fig 1



Fig 2.



Fig 3



Fig 4

obtained in guinea-pigs submitted to the action of different ototoxins, which could also be a contribution to Dohlman's theory In order to avoid possible errors inherent in the animal employed or in the ototoxins or the histochemical techniques of staining, we have radically changed the previous working plan We have used the S^{35} to identify the mucopolysaccharides We wished to eliminate some of the functions of the internal ear, but we did not want to employ aggressive means that could harm other structures or alter biochemical mechanisms hitherto not sufficiently known and so lead to results that would not reflect the lack of function but an alteration of the mechanisms or harmed structures We further thought that it would be advantageous to use embryos, a stage of the animal's life in which there can be no audition since there is no transmission of the sound as the middle ear is not ventilated

We chose the chick embryo This material is adequate for the S^{35} application because, as it cannot be eliminated from the egg, only one application permits to maintain high levels in the blood during several days In our case, being interested in the movements of the mucopolysaccharides marked with S^{35} sulfur in different chronological stages, it seems that there is no doubt about the adequacy of the material With a single application it is only necessary to sacrifice the embryos in different periods of time.

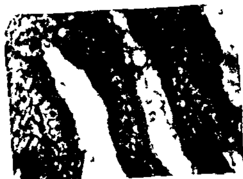


Fig 5

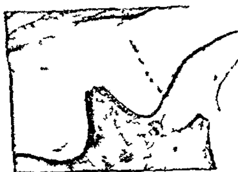


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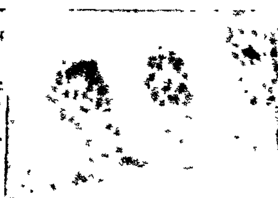


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no auditive function and therefore their ciliated cells do not need sulfomucopolysaccharides since they are to be excited The time differences in the apparition of the granules and in their elimination by the endolymphatic ductus as well can be explained as a lessening of the embryonic circulation

RÉSUMÉ

Les résultats de nos expériences avec S[35] en embryon de poulet sont une contribution à l'hypothèse de Dohlman sur le rôle des sulfomucopolysaccharides dans l'excitation des cellules sensorielles de l'ouïe interne

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Fig 7



Fig 8

autoradiographic study was carried out. The histoautoradiography used has been that of the "stripping film" with Kodak film A R 10 and A R 50, the first having finer grain and therefore less sensibility but a better definition, and the second having a larger grain and more sensibility though less definition which makes it impossible to eliminate the stippling due to background radiation. The exposition time ranged between twenty days and two months. The eggs were injected on the 14th day and opened 6, 12 and 24 hours later.

RESULTS

In order to estimate the results we used the tracheal rings as a control of the caption (Fig 1).

In the eggs sacrificed six hours after the instillation of the S³ solution there is only a zone with S³ in small quantity which corresponds to the tegmentum vasculosum. This can easily be observed in the panoramic view of Fig 2. A higher magnification (Fig 3) shows more clearly the zones with S³ which are around the tegmentum vasculosum. With an even higher magnification the S granules are seen among the tegmentum vasculosum but not in the interior (Fig 4). The vascular conjunctive mesh as well as the epithelium of these mamelons are free of granules (Fig 5). There exists an intense activity at the level of the secretory vestibular epithelium but the tectorial membrane and the cupula are free (Fig 6). At the 12th hour the ampullaceous cupula is densely covered by S granules but the tectorial membrane is free (Fig 7). At the 12th hour the endolymphatic conduit is replete and in this state continues at the 24th hour (Fig 8).

DISCUSSION

Our findings do not coincide with Dohlman's but they are nevertheless a contribution to his ideas. The fact that granules are not found on the tectorial membrane constitutes in our opinion a confirmation of his theory, the chick embryos having not yet ventilated the medium ear have

thesia of the laryngeal, tracheal and bronchial mucous membrane for bronchographic examination Particular interest was concentrated on the time of onset of surface anaesthesia upon the addition of epinephrine

MATERIAL

In this study a total of 189 outpatients, who came to the Clinic for Thoracic Surgery Central Hospital of the University of Helsinki for thorax-surgical consultation was examined The diagnosis when they arrived at the hospital was tumour of the lung or bronchi pulmonary tuberculosis or bronchiectasie These 189 cases comprised 155 male and 34 female patients Their ages varied between 15 and 68 (45 ± 1) years

METHOD

Comparison of Carbocaine Thesat and lidocaine

Bronchographic examination was included in the consultation In order to insert a catheter for x ray examination in the trachea, it is *necessary to anaesthetize the mucous membrane* in the larynx trachea and in both bronchi For this purpose Carbocaine Thesat (4 + 1) % and lidocaine 4% were used In addition these solutions were also used with *an addition of epinephrine* In all cases, the dose was 5 *ml* (200 mg), and the addition of epinephrine was 1 5000 There were thus four different groups in which the first was anaesthetized with Carbocaine Thesat the second with Carbocaine Thesat *with added* epinephrine the third with lidocaine and the fourth with lidocaine with added epinephrine The patients were given slight premedication 45–60 *minutes prior to anaesthetizing* [illegible] – 10 kg These blind

In addition two further *groups* of twenty patients were chosen for testing of the duration This was *done* allowing the catheter to remain in the trachea after the *bronchographic* examination About 30 minutes after administration of the anaesthetic *the catheter* was pushed downwards from where it lay *above the bifurcation so that its tip* irritated the bronchial mucous membrane upon touching *it This* was done at intervals of 5 minutes When the first *coughing reflex occurred* the duration for the case in question was noted

When the time of onset was examined for Carbocaine-Thesat and lidocaine without *epinephrine*, the uvula was first sprayed with *a minimum* dose of Carbocaine Thesat *The reason* for this was to make sure that it would be possible to use an ordinary *larynx mirror* and to place it against the uvula without inducing *irritation when* touching the mucous *membrane* The anaesthetic agent was then filled into a syringe (5 *ml*), *fitted*

A COMPARISON OF CARBOCAINE-THESAT® AND LIDOCAINE AS SURFACE ANAESTHETICS FOR THE LOWER RESPIRATORY TRACT

LEO TIILIVUO
Helsinki, Finland

From the Clinic for Thoracic Surgery (Head Prof. O Peräsalo), Central Hospital of University of Helsinki

In this study, 189 patients were anaesthetized with local anaesthetics for bronchographic x-ray examination Carbocaine Thesat (1+1)% and lidocaine (4%) were compared in a double blind test. The anaesthetic solutions were used both with and without epinephrine There was no difference between Carbocaine-Thesat and lidocaine in the onset of anaesthesia When the group without epinephrine in the anaesthetic solution was compared with the epinephrine group the difference was significant ($p < 0.01$) If epinephrine is added the onset of anaesthesia is slower on the tracheal mucosa The durations of anaesthesia without epinephrine in the local anaesthetic solutions were compared The mean for Carbocaine Thesat was 61 minutes and for lidocaine 102 minutes The results seem to suggest that it is not advisable to add vasoconstrictors to local anaesthetic solutions for surface anaesthesia of the lower respiratory tract

During recent years, Carbocaine and lidocaine have been studied and compared as local anaesthetics rather frequently Most of these investigations have been concentrated on nerve infiltrations and blocks The duration and the toxicity have also been studied in various animal experiments On the other hand, no appreciable research has been devoted to the surface-anaesthetic effect of Carbocaine and lidocaine on the human being, and it was first considered that neither of these substances is a pronounced surface anaesthetic However, Luduena (1960) has found, in a corneal test on rabbits, that the effect of Carbocaine is equal to that of cocaine

In the various preparations available for surface anaesthesia, lidocaine is used alone, whereas Carbocaine has been combined with another surface-anaesthetically active substance, Thesat® This substance is characterized by a high surface-tension reducing effect, it is scarcely toxic but locally irritating in higher concentrations

In the study now being described, a comparison was made between Carbocaine-Thesat and lidocaine with and without epinephrine for anaes-

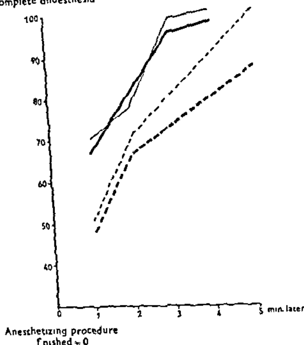


Fig 1 Time of onset —— Carbocaine Thesat - - - Carbocaine Thesat with epinephrine, —— Lidocaine - - - Lidocaine with epinephrine

ing procedure One minute later, only 20 still coughed, while 5 minutes after the completion of the spraying 8 still coughed when the catheter was moved in the trachea

These results are presented as figures and percentages in Table 1 It can be seen that there is no difference between Carbocaine-Thesat and lidocaine or between Carbocaine-Thesat + epinephrine and lidocaine + epinephrine If the Carbocaine-Thesat and Carbocaine-Thesat + epinephrine groups are compared statistically (Table 2), the difference is almost significant (0 1 > *p*

Table 1 *Time of onset*

Preparation	N	Disappearance of cough reflex (min) 0–1	1 2	2 3	3–4	4 5	5
Carbocaine Thesat (4 + 1)%	46	32	4	9	1	—	—
Lidocaine 4%	43	29	6	6	1	—	1
Carbocaine Thesat (4 + 1)% with epinephrine 1 5000	39	20	8	—	—	11	—
Lidocaine 4% with epinephrine 1 5000	61	29	12	—	—	12	8

with a long, bent application nozzle. When the epiglottis and vocal cords could be clearly seen, 1 ml of the anaesthetic was sprayed on the rear side of the epiglottis, whereupon some of it ran down into the larynx. The remainder was sprayed in two or three turns down in the trachea, whereupon the patient was told to hold his breath, thus closing the gorge when he began to cough. An attempt was thus made to obtain an even dispersal of the anaesthetic. This procedure took 2 minutes, almost regularly. When the entire amount of anaesthetic had been administered, a pause was made for one minute and the x-ray catheter was inserted down into the trachea. In order to get an idea of the time of onset, a note was made of how many of the patients who coughed when the catheter was pushed down in the trachea. When the catheter had been placed in the trachea, a note was made of how many patients were still coughing 1 minute later. All the cases which coughed when the catheter was inserted, were checked until anaesthesia set on with disappearance of the coughing reflex when the catheter was moved up and down in the trachea and principal bronchi.

For statistical purpose, a comparison was made between the group which had complete anaesthesia 1 minute after the actual anaesthetizing procedure with the rest of the cases in the group concerned.

RESULTS

In a group of 46 patients (age 46±2), Carbocaine-Thesat was used without epinephrine as the local anaesthetic agent for surface anaesthesia of the trachea. Lidocaine was used for the same purpose, in the same concentration (4%) for 43 patients (age 43±2).

Time of onset for Carbocaine-Thesat (4+1)%. In the Carbocaine group 14 cases were considered negative, i.e. they coughed when the catheter was introduced into the trachea. Four of these did not cough 1 minute later, 9 did not cough 2 minutes later and in the last one the cough reflex disappeared after 3 minutes from the introduction of the catheter.

Time of onset for lidocaine 4%. In the lidocaine group, 14 out of 43 cases were considered negative. Six of these lost the cough reflex 1 minute after the introduction of the catheter, 6 after 2 minutes, 1 after 3 minutes and one finally *10 minutes after the placing of the catheter.*

Time of onset for Carbocaine-Thesat (4+1)% with epinephrine 1: 5000. Carbocaine Thesat with epinephrine in a concentration of 1: 5000 was next used in exactly the same way as that described above, in 39 cases (age 44±2). Of these, 20 did not cough after 1 minute after spraying of the anaesthetic, 8 more after 2 minutes, and the remaining 11 were completely anaesthetized after a 5-minute interval.

Time of onset for lidocaine (4%) with epinephrine 1: 5000. When epinephrine was added to lidocaine and used in 61 cases (age 45±2), 32 were regarded as negative 1 minute after the termination of the anaesthetiz-

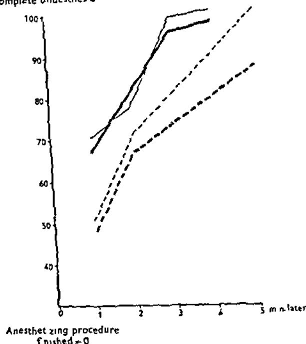


Fig. 1. *Time of onset* —— Carbocaine Thesat - - - Carbocaine Thesat with epinephrine
—— Lidocaine - - - Lidocaine with epinephrine

ing procedure. One minute later, only 20 still coughed, while 5 minutes after the completion of the spraying 8 still coughed when the catheter was moved in the trachea.

These results are presented as figures and percentages in Table 1. It can be seen that there is no difference between Carbocaine-Thesat and lidocaine or between Carbocaine-Thesat + epinephrine and lidocaine + epinephrine. If the Carbocaine Thesat and Carbocaine-Thesat + *epinephrine* groups are compared statistically (Table 2) the difference is almost significant ($0.1 > p$

TABLE 1. *Time of onset*

Preparation	N	Disappearance of cough reflex (min.)					
		0–1	1–2	2–3	3–4	4–5	5
Carbocaine Thesat (4+1)%	46	32	4	9	1	—	—
Lidocaine 4%	43	29	6	6	1	—	1
Carbocaine Thesat (4+1)% with epinephrine 1:5000	39	20	8	—	—	11	—
Lidocaine 4% with epinephrine 1:5000	61	29	12	—	—	12	8

TABLE 2. *Frequency of anaesthesia after one minute.*

Carbocaine-Thesal and lidocaine used for surface anaesthesia of the lower respiratory tract with and without epinephrine. The results are presented as numbers of cases and percentages. The results of statistical treatment are also shown. When the groups in which local anaesthetic only was used are compared with the groups in which epinephrine was added, the difference is significant ($p < 0.01$). The conclusion is that the vasoconstrictor has a retarding effect on the onset of anaesthesia.

Preparation	Complete anaesthesia	Coughing after 1 min	Total
1 Carbocaine-Thesal (4+1)%	32 (70%)	14 (30%)	46
2 Same, plus epinephrine 1:5000	20 (51%)	19 (49%)	39
3 Lidocaine 4%	29 (67%)	14 (33%)	43
4 Same, plus epinephrine 1:5000	29 (48%)	32 (52%)	61
1–2 $\chi^2 = 2.97$, $0.10 > p > 0.05$			
3–4 $\chi^2 = 1.05$, $p > 0.05$			

TABLE 3. *Onset time (min) ± s.e.*

1	Carbocaine-Thesal (4+1)%, $N = 46$	1.5 ± 0.1	$p < 0.01$
2	Same, plus epinephrine 1:5000, $N = 39$	2.3 ± 0.3	
3	Lidocaine 4%, $N = 43$	1.7 ± 0.3	$p < 0.02$
4	Same, plus epinephrine 1:5000, $N = 61$	2.6 ± 0.3	
5	= 1 + 3, $N = 89$	1.6 ± 0.1	$p < 0.001$
6	= 2 + 4, $N = 100$	2.5 ± 0.2	

> 0.05). With the results 30 per cent negative without epinephrine and 49 per cent with epinephrine, there is a suggestion that the vasoconstrictor has a retarding effect. Campbell & Adriani (1958) have reported that vasoconstrictors have no effect when surface anaesthesia is induced, since the resorption of the agent into the circulation is not affected.

The comparative negative figures for lidocaine-anaesthetized patients are 33 per cent with lidocaine alone and 52 per cent with lidocaine + epinephrine. The difference is here significant ($p < 0.05$).

When the duration of the surface anaesthesia of the trachea was studied in two groups of 20 patients, it was found that with Carbocaine-Thesal the mean duration was 61 minutes. With lidocaine the corresponding mean duration was 102 minutes. The difference between these groups is highly statistically significant ($p < 0.001$). The anaesthetic solutions used were without epinephrine.

DISCUSSION

In the clinical use of local anaesthetics, intratracheal application is of special interest. According to Adriani, the tracheal mucosa absorption of

local anaesthetic is almost as rapid as an intravenous injection. The curves of drug level in the blood after a surface application resemble nearly those of a rapid intravenous injection. Peaks are lower, take longer to develop and do not rise so abruptly but within four to six minutes the peak is one third to one half that obtained after a rapid intravenous injection when an equivalent dose is applied to the pyriform fossae. Absorption according to Adriani (1959) is more rapid from the trachea than from the pharynx.

On the other hand Campbell & Adriani (1958) have stated that since vasoconstrictors are effective for infiltration, nerve blocking and spinal anaesthesia it would not seem unreasonable to assume that they are also effective in retarding absorption from mucous membranes. This however is not so. The difference in blood drug levels after the application of tetracaine and cocaine to the pyriform fossae and trachea with and without epinephrine were not significant. After preliminary spraying with epinephrine and arterenol in sufficient quantities to cause blanching of the mucous membranes, the drug levels after the application of either drug were almost the same as those of the controls.

In the study now being reported the effect on time of onset of epinephrine added to Carbocaine Thesat or lidocaine seemed to be inhibitory. The difference was significant ($p < 0.01$). This is valid both for the frequency of onset within one minute ($p < 0.01$) and for the time of onset ($p < 0.001$) (Table 3). It can anyhow be stated that there was no benefit from adding epinephrine, as the patients were anaesthetized more slowly with a vasoconstrictor added to the local anaesthetic solution. The duration of Carbocaine Thesat averaged 61 *minutes*, which is quite enough for a bronchographic x-ray examination. The corresponding lidocaine duration was 102 *minutes* without epinephrine. Lechat & Delaux (1961) studied the potentiating effect of chloropromazine on local anaesthetics. In their experiment the mean duration of the anaesthesia of the cornea in 8 rabbits was 61 *minutes* with 1 *per cent* Carbocaine (without Thesat) and 110 minutes with 1 *per cent* lidocaine. These are very close to the corresponding figures in the present study for mean durations of tracheal mucosa surface anaesthesia with Carbocaine Thesat and lidocaine but performed on man.

It has already been mentioned that the total amount of local anaesthetic used in this study was 200 mg for each case. This was well tolerated both with and without epinephrine. Neither Carbocaine Thesat nor lidocaine seemed to have any side effects. In all cases an adequate anaesthesia was obtained although there was a difference in the speed of onset of complete anaesthesia from case to case.

In the length of time for onset of anaesthesia the agents were equal and no statistical difference is visible. The only difference which was also statistically significant was that for duration. The duration when epinephrine was added to the local anaesthetic was not studied as Adriani (1959) has already stated that there will be no difference when the trachea

TABLE 2 *Frequency of anaesthesia after one minute*

Carbocaine Thesat and lidocaine used for surface anaesthesia of the lower respiratory tract with and without epinephrine The results are presented as numbers of cases and percentages The results of statistical treatment are also shown When the groups in which local anaesthetic only was used are compared with the groups in which epinephrine was added, the difference is significant ($p < 0.01$) The conclusion is that the vasoconstrictor has a retarding effect on the onset of anaesthesia

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1–2 $\chi^2 = 2.97$, $0.10 > p > 0.05$
3–4 $\chi^2 = 4.05$ $p > 0.05$

TABLE 3 *Onset time (min.)* $\pm$ *s.e.*

1 Carbocaine Thesat (1+1)%, $N = 46$	1.5 ± 0.1	$p < 0.01$
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HEREDITARY HEMORRHAGIC TELANGIECTASIA

Effective Treatment of Epistaxis by Septal Dermoplasty

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From the Department of Otolaryngology, University Hospital, Columbus 10

The severe, sometimes daily, nosebleeds of patients with hereditary hemorrhagic telangiectasia can now be controlled effectively by a surgical procedure called septal dermoplasty. In this operation the principle is to replace the fragile epithelium in the anterior one third of the nose by a split thickness graft of skin from the thigh. The skin graft being tough resists trauma and prevents bleeding. Results in over 100 patients demonstrate that the procedure is effective. Some patients never bleed again while others who do bleed occasionally, do so much less severely and less often. Other uses for the septal dermoplasty operation include closure of septal perforations, treatment of chronic septal ulceration, and reconstruction of the septum after removal of certain tumors.

Hereditary hemorrhagic telangiectasia or Weber-Osler-Rendu disease, originally described by Babington in 1865, causes epistaxis as its cardinal symptom. Transmitted as a Mendelian dominant characteristic, the disorder affects fifty per cent of siblings and may even be lethal when both parents have the disease. Nosebleeds suffered by these patients are *frequently* of heroic proportions; some patients have received as many as 2000 transfusions during their lifetimes. As one of Osler's patients *put it*: I am in the habit of bleeding to death every day. Others who bleed in lesser amounts still may be handicapped seriously because they bleed so frequently that their social and economic pursuits are curtailed.

The disease of course is *not limited* to the nasal mucosa—virtually every body surface and most visceral organs may be affected. Except rarely, however, solid organs which have been found to contain telangiectases do not bleed nor [illegible] those of the ureter, meninges [illegible] there is no trauma to precipit[illegible] hemorrhage. Bleeding occurs chiefly from those epithelial surfaces where *trauma is likely* and where the mucosa is not of *squamous type*. In short, patients with *hereditary* hemorrhagic telangiectasia bleed from their noses and less frequently from their gastrointestinal tracts. In both of these situations there is frequent trauma (even though minimal) to relatively fragile mucous membranes and the mucous membrane of

is being examined Schon (1961) mentioned that it is dangerous to use epinephrine with local anaesthetics for surface anaesthesia, since he observed that epinephrine enlarged the vessels in tracheal mucosa

ZUSAMMENFASSUNG

Die ortlichen Betaubungsmittel Carbocain-Thesat (4+1%) und Lidocain 4% wurden im Doppelblindversuch miteinander verglichen Die beiden Mittel wurden mit und ohne Adrenalinzusatz zur Oberflachenanasthesie bei 189 Patienten zwecks *Durchfuhrung einer Bronchographie angewandt. Die Wirkung von Carbo*cain-Thesat und Lidocain setzte nach ungefahr gleich langer Latenzzeit ein Durch Adrenalinzusats wurde der Wirkungseintritt beider Mittel auf der Trachealschleimhaut signifikant verzogert ($p<0{,}01$) Die mittlere Anasthesiedauer fur Carbocain-Thesat ohne Adrenalin betrug 61 Minuten, fur Lidocain ohne Adrenalin 102 Minuten Den Ergebnissen zufolge erscheint es ratsam, Lokalanasthetica ohne Zusatz von vasokonstriktorischen Mitteln zur Oberflachenbetaubung der unteren *Atemwege zu benutzen*

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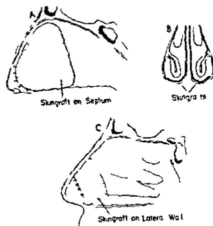


FIG. 1 A Graft in place on anterior one third of septum This graft must also cover the floor of the nose and if the surgeon wishes it may be carried across the floor and up the lateral wall as one piece of skin

B Both sides of septum are grafted at same operation As explained under A if the surgeon wishes he may extend these grafts up onto the lateral walls of the nose—rather than placing separate grafts as shown in C

C Showing a separately placed graft on the lateral nasal wall where it covers the anterior part of the inferior turbinate Grafts are carefully sewn to cut margins of vestibular skin so that they will not be displaced when packing is placed

the intranasal appearances approximate those of the normal nasal vestibule Crusting is ordinarily no problem or at least it is no more of a problem than it would be in any patient who fails to blow his nose, and patients with hereditary hemorrhagic telangiectasia seldom blow their noses for fear of starting nosebleeds

2 *The technique* Under local anesthesia (about 25 30 cc of one per cent Xylocaine) a split thickness graft measured on the Brown electric dermatome as 18–20/1000 inch is removed from the anterior thigh (A hairless site need *not* be selected since hair does not grow in this graft) The graft is preserved in a saline soaked sponge and the donor site dressed with Adaptic gauze over which are placed several dry gauze sponges The donor site heals in four to six weeks

The intranasal operation also is done under local anesthesia Five per cent cocaine or one per cent pontocaine applied topically serves as anesthesia for the mucous membrane Additional infiltration of *one* percent Xylocaine with 1–50 000 epinephrine may assist in controlling bleeding The Xylocaine solution is also used to infiltrate the *entire* lower end of the nose and the adjacent upper lip

A curved incision is made to separate each nasal ala from the upper lip This incision permits retraction of the ala and affords better visualization of the interior of the *nose* Later it is closed with 5 0 nylon suture Often there is adequate working room without the preliminary alar incisions,

the nose, being more fragile than that of the gastrointestinal tract, bleeds far more often. In contrast, the finger pads, which almost invariably show telangiectases, rarely, if ever, bleed because they are protected by skin, a tough epithelium designed to resist trauma. Similarly the mucous membrane of the oral cavity, especially that of the tongue and lips, although often the site of telangiectases, seldom bleeds since squamous mucosa protects it efficiently.

The characteristic lesion in hereditary hemorrhagic telangiectasia is a tiny arteriovenous fistula. The lesions appear cherry red. They are flat or only slightly elevated on the skin, but often papular in the thin nasal mucosa.

It is important to emphasize that in hereditary hemorrhagic telangiectasia the patient's blood is normal (except for anemia) and that the only defect is in the blood vessel. The management of epistaxis is based on that fact.

Many different forms of medical and surgical therapy have been tried in futile efforts to control the severe, often daily epistaxis of patients with hereditary hemorrhagic telangiectasia. For example, ligation of either the external carotid or ethmoidal arteries, or both, has been done but to no avail, submucous resection of the septum and even total septectomy is practiced, electrical or chemical cautery and the injection of sclerosing solutions is common practice. Radium applicators applied to the nasal mucosa, a treatment in vogue two or three decades ago, almost invariably resulted in septal perforation. After any of these treatments bleeding was apt to be worsened since the telangiectases reappeared and then in epithelium that was more friable than ever.

Medical treatment, while usually not worsening things, seldom helped. For example, snake venom, rutin, vitamin K, and Adrenosem are drugs that either were or still are commonly used. Premarin has been a favorite remedy and is recommended on the assumption that it produces metaplasia in nasal mucosa by converting the normal respiratory mucosa to a squamous mucosa. If this does occur it is the exception rather than the rule.

Septal Dermoplasty

1. *The principle.* Originally conceived as a method of closing a septal perforation, septal dermoplasty has found greater use in treatment of epistaxis caused by hereditary hemorrhagic telangiectasia. The *principle* is that of replacing the fragile respiratory epithelium of the anterior part of the nose with a split thickness skin graft. The skin graft, being tough, resists trauma and thereby prevents bleeding. Because of the superb blood supply provided by the underlying perichondrium and the excellent opportunity for packing virtually all grafts take. The procedure may be regarded as one which extends the vestibular skin posteriorly along the nasal septum as well as along the floor and lateral walls of the nose. After septal dermoplasty, except that there is no hair in the new skin,

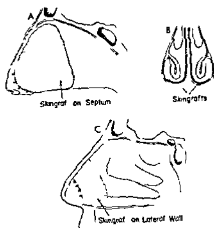


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but these incisions, which heal without a scar, should not be neglected when needed

The mucosa of both sides of the nasal septum, floor of the nose, and interior aspects of the lateral walls is removed with a curette The mucosa scrapes off easily leaving underneath a vascular, but not readily bleeding, layer of perichondrium *It is very important not to remove perichondrium* or to separate it from the septal cartilage since it is this layer that must nourish the new grafts, also perichondrium must continue to nourish the septal cartilage When all mucosa has been carefully removed there is a denuded surface in the entire anterior aspect of the nose, bilaterally, extending somewhat further posteriorly on the septum than on the lateral walls Next, a narrow strip of vestibular skin is excised from the septum and from the lower margin of the upper lateral cartilage

The skin graft is then cut in two and one piece used in each side of the nose Each piece can again be divided and one section applied to the nasal septum and floor, and the other to the lateral wall, or a single piece (one-half of the entire graft) can be draped from the very top of the septum downward across the floor and up the lateral wall In either case it is important to *fix the grafts anteriorly* to the cut edges of the vestibular skin, both on the septum and on the lateral side of the nose Attaching the grafts anteriorly prevents them from being displaced when packing is placed later

Careful and accurate packing is an important step because it is the packing which holds the grafts firmly against their bed If packing is not placed with great care the grafts will be displaced and fail to grow One half inch gauze thoroughly impregnated with an antibiotic ointment such as Terramycin or Neosporin is cut in several pieces and small packs fashioned and placed Packing can be removed safely on the fifth post-operative day because at that time the grafts are well attached

If more skin has been placed than there is denuded area, and that is the usual case, there will be nasal obstruction for several days or weeks Then careful trimming of the excess skin will help clear the nose After a month or two most patients have but minimal trouble with crusting or nasal obstruction

3 *The results* Septal dermoplasty has now been done on more than 100 patients with hereditary hemorrhagic telangiectasia and on some 25 other patients for such conditions as septal perforations that crust and bleed and for chronic ulceration of the nasal septum unresponsive to more conservative therapy The results have been almost uniformly good There is a great reduction in the severity and frequency of nosebleeds A few patients have had no further bleeding after as long as five years In those who may bleed again, a revision of the procedure may be advisable to place skin where, through technical error, it was not placed correctly the first time There seems to be no difficulty in obtaining almost a one-hundred per cent take of the grafted skin—the difficulties are in making

certain that the nasal mucosa is properly removed and that skin and packing are placed accurately

Other uses of septal dermoplasty

1 *Closure of septal perforations* By denuding mucosa widely around the margins of a septal perforation and placing a split thickness skin graft on each side of the septum many small and even moderate size perforations can be closed Of course, *no perforation should be closed unless it causes symptoms* particularly bleeding or bleeding and crusting By operating only those patients who have symptoms good results are achieved even though the skin grafts break down and the perforation reappears The reason is that even if the central part of the skin graft sloughs the margins of the perforation still will be covered by skin and bleeding and crusting controlled After all it is the margins that bleed not the hole As in septal dermoplasty done for hereditary hemorrhagic telangiectasia, one must be careful to scrape off mucosa but leave perichondrium to nourish both the underlying cartilage and the new grafts

2 *Chronic septal ulceration* Occasionally a patient is seen with an ulcer of the nasal septum which fails to heal or to stay healed in spite of all types of medical therapy Then a limited septal dermoplasty is indicated on the ulcerated side of the septum only The substitution of tough skin for the fragile and infected mucosa corrects the condition permanently

3 *After resection of tumor* Sometimes a neoplasm is present on one side of the septum that does not invade the entire septum and the opposite mucoperichondrium The septum with the exception of mucoperichondrium on the involved side may be resected and a skin graft substituted Of course the raw surface of the mucoperichondrium even if not grafted eventually heals but it does so slowly Septal dermoplasty provides for quicker healing and also prevents septal perforation if there has been a tear in the single remaining sheet of mucoperichondrium

ZUSAMMENFASSUNG

Die starken manchmal täglich vorkommenden Nasenbluten *die bei* hereditärer hämorrhagischer Telangiektasie der Fall sind können nun sehr wirkungsvoll chirurgisch beseitigt oder wenigstens vermindert werden Diese Operation wird Dermplastik des Nasenseptums genannt Bei diesem Verfahren handelt es sich prinzipiell darum dass die zarte Schleimhaut im vorderen Drittel der Nase mit einem freien Hautlappen nach Thiersch (split thickness) versehen wird Dieser Hautlappen wird vom Schenkel genommen Das Transplantat ist widerstandsfähiger gegen Traumen und das Bluten ist dadurch verhindert Die Ergebnisse bei 100 Patienten beweisen dass dieses Verfahren wirksam ist Viele Patienten bluten überhaupt nicht mehr während andere nur noch vereinzelt und sehr vermindert bluten Dieselbe Operation kann auch angewandt werden um Septumperforationen zu schliessen oder auch gegen chronische Geschwüre Auch zur Wiederformung des Nasenseptums nach Entfernung eines Tumors eignet sich [illegible]

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NICHTWAHRNEHMUNG DER AUGENBEWEGUNGEN UND CORNEO-CONJUNCTIVALE ENTSTEHUNG DES SUBJEKTIVEN AUGENZUGES BEIM VESTIBULAREN NYSTAGMUS

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28 gesunde nichteingeweihte Versuchspersonen wurden bei 110 Drehprüfungen im Dunkelraum mit Nystagmusregistrierung per- und postrotatorisch nach Wahrnehmung von Augenbewegungen *befragt. Bei intakter* Sensibilität der Augenbindehaut wurde während des vestibulären Nystagmus in rund $^2/_3$ der Versuche keinerlei Augenbewegung wahrgenommen. In 17% spürten die Versuchspersonen einen einseitig gerichteten Augenzug, signifikant häufiger (13%) zur Seite *der langsamen* Nystagmusphasen. In 11% wurden rhythmische rasche Augenbewegungen empfunden, nur insignifikant häufiger in Richtung *der raschen* Nystagmusphasen. Es machte keinen Unterschied aus, ob die Augen dabei offen oder geschlossen waren. Nach Anaesthesie der *Conjunctiva und* Cornea wurde während des *vestibulären* Nystagmus keinerlei Augenbewegung mehr wahrgenommen. Diese Befunde passen zum *Fehlen einer* nystagmussynchronen Entladungsrhythmik von Großhirnneuronen der *Katze während* des vestibulären Nystagmus bei Ausschluß des Sehens und sie bestätigen, daß die Propriozeptoren der Augenmuskeln zur Vermittlung der Wahrnehmung von Augenbewegungen nicht ausreichen.

EINLEITUNG

Bei experimentellen Labyrinthprüfungen, die im Dunkelraum oder bei geschlossenen Augen vorgenommen werden, bemerken Patienten meist keine Augenbewegungen, obwohl die Drehbeschleunigung ... und deren Richtung ... und nach mehr ... Fuhe ... ugenbewegungen meist ... kt. Diese Beobachtung entspricht der schon von Helmholtz beschriebenen Erfahrung, daß wir passive Augenbewegungen nicht wahrnehmen können.

In dieser Arbeit wird untersucht, ob gesunde Menschen in der Lage sind

bei Ausschluß des Sehens ihre vestibulären Augenbewegungen und deren Richtung wahrzunehmen und welche Rolle die Sensibilität der Conjunctiva und Cornea dabei spielt.

METHODIK

Die Versuche wurden mit dem Tönnies'schen elektronisch gesteuerten Drehstuhl ausgeführt, der konstante Beschleunigungen anzuwenden gestattet. Die Augenbewegungen wurden in horizontaler und vertikaler Komponente elektrisch registriert (Methodik siehe Jung & Tönnies 1948).

In einer ersten Versuchsreihe wurden 18 Vpn, die keine Kenntnis über vestibuläre Augenbewegungen besaßen, im völlig verdunkelten Raum erst bei geöffneten und dann bei geschlossenen Augen ohne Anaesthesie der Conjunctiva mit einer Winkelbeschleunigung von 1°/sec² nach beiden Seiten angedreht und dann aus einer Drehgeschwindigkeit von 90°/sec gestoppt. Während der Beschleunigung und nach dem Stop wurden die Vpn nach Wahrnehmung von Augenbewegungen und deren Richtung gefragt. Die Drehbeschleunigung von 1°/sec² ist überschwellig; bei Gesunden tritt Nystagmus auf. Mit diesen 18 Vpn wurden insgesamt 70 Drehungen angestellt, wobei die per- und postrotatorischen Wahrnehmungen der Versuchspersonen gesondert ausgewertet wurden.

In einer zweiten Versuchsreihe wurde der Einfluß der Sensibilität der Conjunctiva und Cornea auf die Wahrnehmung der Augenbewegungen beim Nystagmus geprüft. Bei 10 neuen, nicht eingeweihten Versuchspersonen wurden zuerst ohne und dann mit beidseitiger Anaesthesie der Conjunctiva Rechts- und Linksdrehungen mit 1°/sec² Beschleunigung und Stop aus 90°/sec ausgeführt, insgesamt also 40 Drehungen. Da sich in der ersten Serie kein Einfluß von Lidöffnung und Lidschluß ergeben hatte, wurde die zweite nur mit geschlossenen Augen im Dunkelraum geprüft. Zur Conjunctivalanaesthesie wurden je Auge 2 Tropfen Novesin® (0,4%ige Lösung) und 1 Tropfen Pantocain® (1%ige Lösung) verwandt. Der Nystagmus wurde registriert. Per- und postrotatorisch wurde gesondert nach der Wahrnehmung von Augenbewegungen gefragt, insgesamt also 80 mal.

ERGEBNISSE

Erste Versuchsreihe
Drehbeschleunigung im Dunkeln ohne Anaesthesie der Conjunctiva

In etwa *zwei Drittel* (63,6%) der 140 Einzelversuche gaben die 18 Vpn an, sie spürten *keinerlei Augenbewegungen*. In 13,8% (= 19mal) wurde ein *Zug der Augen in die Richtung der langsamen Phase bemerkt*. Auch ein Zug in der Richtung der schnellen Phase wurde vereinzelt angegeben; er trat nur postrotatorisch in 4,3% (= 6mal) der Versuche auf. Nimmt man die Resultate ohne Anaesthesie aus der zweiten Versuchsreihe (siehe unten) dazu, in der bei 40 Versuchen 5 mal Augenzug in Richtung der langsamen Phase, 1 einmal in Gegenrichtung angegeben wurde, so ergibt sich ein Verhältnis von 24:6. Diese größere Häufigkeit wahrgenommenen Augenzuges

TABELLE 1 *Erste Versuchsreihe Wahrnehmung von Augenbewegungen während des vestibulären Nystagmus ohne Anaesthesie der Conjunctiva*

18 Versuchspersonen 140 Versuche Untersuchung im Dunkelraum bei geöffneten und geschlossenen Augen

Art der bemerkten Augenbewegung	Augen geschlossen		Augen geöffnet		Summe
	perrotat	postrotat	perrotat	postrotat	
Augenruhe	29	18	23	19	89
Augenzug in Richtung der langsamen Nystagmusphasen	2	5	6	6	19
Augenzug in Richtung der schnellen Nystagmusphasen		4		2	6
Rhythmische Augenzuckungen in Richtung der raschen Nystagmusphasen	2	1	3	5	11
Rhythmische Augenzuckungen in Richtung der langsamen Nystagmusphasen		2		2	4
Unrhythmische Augenbewegungen	3	6	2		11

in Richtung der langsamen Nystagmusphasen ist signifikant (Chi-Quadrat-Methode $p = 0{,}02$) Am häufigsten war aber, daß keinerlei Augenbewegungen wahrgenommen wurde, obwohl die *Richtung der Drehbeschleunigung* des ganzen Leibes *richtig empfunden* wurde und Nystagmusamplituden bis 30° auftraten

In 7,9% der Versuche nahmen die Vpn *unrhythmische*, mit Intervallen auftretende Bulbusexkursionen wahr Sie wurden *oft als vertikale* oder diagonale Augenbewegungen, auch als binokular unkoordinierte Exkursionen geschildert

Nur vereinzelt wurden rhythmische Augenbewegungen wahrgenommen, fast immer als horizontal In Richtung der zu erwartenden schnellen Phase waren sie häufiger (*11mal* = *7,8%*) als in Richtung der langsamen Phase (*4mal* = *2,8%*) Dieser Unterschied der Richtung ist *insignifikant*, auch wenn man die Ergebnisse ohne Conjunctiva-Anaesthesie aus der *zweiten* Versuchsreihe dazuzählt *es ergibt sich* dann ein Verhältnis von 14 5, das eine Wahrscheinlichkeit von ~ 0 15 für zufälliges Vorkommen hat

Ob die Augen bei der Untersuchung geschlossen oder geöffnet waren (in jedem Fall im Dunkelraum) beeinflußte die Ergebnisse nicht Auch war die Wahrnehmung von Augenbewegungen perrotatorisch und postrotatorisch etwa gleich selten

Hinsichtlich der Neigung einer Person, rhythmische oder unrhythmische Augenbewegungen wahrzunehmen, ergab sich keine Regel 7 von der 18 Vpn der ersten Versuchs*gruppe* (davon zwei mehrmals) gaben an, rhythmische Augenbewegungen wahrzunehmen Diese Empfindung war inkonstant und meist schon während der nächsten Versuchsphase trotz ähnlicher Nystagmusintensität nicht mehr vorhanden 5 Vpn gaben immer an, ihre

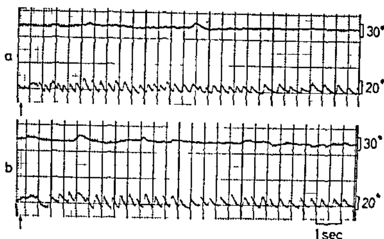


Abb. 1. Kein Einfluß der Anaesthesie des *Conjunktivalsackes auf den postrotatorischen Nystagmus.* Die Versuchsperson bemerkte weder mit noch ohne die Lokalanaesthesie ihre Augenbewegungen (Amplituden bis 20°) während des Nystagmus. *a)* vor der Anaesthesie, *b)* nach Anaesthesie von Conjunctiva und Cornea. Jeweils obere Kurve vertikale, untere horizontale Bewegungskomponente (hier postrotatorischer Nystagmus nach rechts). Stop bei Pfeil aus Linksdrehung 90°/sec. ENG Nr. 471/64

Augen verhielten sich ruhig. 6 Vpn verspürten einen „*Augenzug*", nahmen aber nie rhythmische Augenbewegungen wahr. Nur selten gab dieselbe Vp während verschiedener Versuchsphasen einmal einen Zug, das andere Mal rasche Augenbewegungen an.

Zweite Versuchsreihe
Einfluß der Anaesthesie von Conjunctiva und Cornea

Von den 10 Versuchspersonen dieser Serie bemerkten 5 ohne und mit Anaesthesie nie ihre *Augenbewegungen während des vestibulären Nystagmus.* In rund drei Viertel (29/40) der Versuche ohne Anaesthesie wurde trotz des ablaufenden Nystagmus Augenruhe empfunden (vgl. Tab. 2). Die anderen 5 Versuchspersonen *bemerkten bei intakter Sensibilität der Conjunctiva* gelegentlich verschiedene Arten von *Augenbewegungen* während des Nystagmus, *nach Anaesthesie der Conjunctiva hingegen keinerlei Augenbewegung* mehr.

Die von diesen 5 Vpn vor der Anaesthesie wahrgenommenen *Augenbewegungen während des vestibulären Nystagmus* verteilten sich wie folgt:

2 verspürten nur unregelmäßige, teilweise binocular unkoordinierte Augenbewegungen. 2 Vpn nahmen Nystagmus wahr, eine davon häufiger nur einen Augenzug in *Richtung der langsamen Phasen.* 1 *Versuchsperson spürte* nur diesen Zug in Richtung der langsamen Nystagmusphasen (vgl. Tab. 2). Man hatte den Eindruck, daß Versuchspersonen von hoher Intelligenz ihre Augenbewegungen leichter bemerkten.

Amplituden und Intervallverteilung der Nystagmusschläge änderten sich durch die Anaesthesie des Conjunctivalsackes nicht (Abb. 1).

TABELLE 2. Zweite Versuchsreihe. *Wahrnehmung von Augenbewegungen während des vestibulären Nystagmus ohne und mit Anaesthesie der Conjunctiva und Cornea*

10 Versuchspersonen, 80 Versuche, 40 ohne und 40 mit Anaesthesie. Untersuchung im Dunkelraum bei geschlossenen Augen

Art der bemerkten Augenbewegung	Ohne Anaesthesie der Conjunctiva		Summe	Conjunctiva anaesthesiert		Summe
	perrotat	postrotat		perrotat	postrotat	
Augenruhe	15	14	29	20	20	40
Augenzug in Richtung der langsamen Nystagmusphasen	2	3	5			
Augenzug in Richtung der schnellen Nystagmusphasen			0			
Rhythmische Augenzuckungen in Richtung der raschen Nystagmusphasen	1	2	3			
Rhythmische Augenzuckungen in Richtung der langsamen Nystagmusphasen		1	1			
Unrhythmische Augenbewegungen	2		2			

DISKUSSION

Obwohl es jetzt sicher ist, daß die Augenmuskeln auch die menschlichen sensorische Organe (Muskelspindeln, Sehnenorgane und freie sensorische Nervenendigungen) enthalten (Cooper & Daniel 1949, Cooper *et al.* 1955, Whitteridge 1960), hat der Mensch doch keinen bewußten Lagesinn der Augen (Helmholtz 1867, Brindley & Merton 1960, Merton 1964). Die propriozeptive Afferenz aus den Augenmuskeln, die großenteils über den N. trigeminus (Cooper *et al.* 1955), teilweise aber wahrscheinlich auch über die Augenmuskelnerven selbst zum Hirnstamm geleitet wird (Bach-y-Rita *et al.* 1963), dient offenbar nicht der Lagewahrnehmung der Augen oder der visuellen Richtungslokalisation und Raumkonstanz der Sehdinge, sondern einem untergeordneten Regelkreis Augenmuskel–Hirnstamm–Augenmuskel, der für die automatische Ausführung der übergeordneten (visuellen, vestibulären und willkürlichen) Blickkommandos sorgt (Vossius 1961).

Einen ersten Hinweis darauf, daß auch die raschen Phasen des vestibulären Nystagmus bei Ausschluß visueller Afferenz nicht zum Großhirn gemeldet werden, ergaben Untersuchungen über die Antworten einzelner Nervenzellen zahlreicher Großhirnrindenfelder der Katze auf vestibuläre Reize (Kornhuber & Fonseca 1964).

Im Gegensatz zu Neuronen der Vestibulariskerne und der Formatio [illegible]ns zeigen corticale Neurone bei Ausschluß des

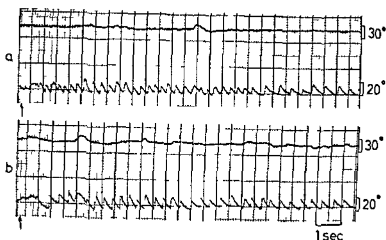


Abb. 1. Kein Einfluß der Anaesthesie des Conjunktivalsackes auf den postrotatorischen Nystagmus. Die Versuchsperson bemerkte weder mit noch ohne die Lokalanaesthesie ihre *Augenbewegungen (Amplituden bis 20°)* während des Nystagmus. *a)* vor der Anaesthesie, *b)* nach Anaesthesie von Conjunctiva und Cornea. Jeweils obere Kurve vertikale, untere horizontale Bewegungskomponente (hier postrotatorischer Nystagmus nach rechts). Stop bei Pfeil aus Linksdrehung 90°/sec. ENG Nr. 4/1/64.

Augen verhielten sich ruhig. 6 Vpn verspürten einen „*Augenzug*", nahmen aber nie rhythmische Augenbewegungen wahr. Nur selten gab dieselbe Vp während verschiedener Versuchsphasen einmal einen Zug, das andere Mal rasche Augenbewegungen an.

Zweite Versuchsreihe
Einfluß der Anaesthesie von Conjunctiva und Cornea

Von den 10 Versuchspersonen dieser Serie bemerkten 5 ohne und mit Anaesthesie nie ihre Augenbewegungen während des vestibulären Nystagmus. *In rund drei Viertel (29/40) der Versuche ohne Anaesthesie wurde* trotz des ablaufenden Nystagmus Augenruhe empfunden (vgl. Tab. 2). Die anderen 5 Versuchspersonen *bemerkten bei intakter Sensibilität der Conjunctiva* gelegentlich verschiedene Arten von *Augenbewegungen* während des Nystagmus, *nach Anaesthesie der Conjunctiva hingegen keinerlei Augenbewegung* mehr.

Die von diesen 5 Vpn *vor der Anaesthesie wahrgenommenen Augenbewegungen* während des vestibulären Nystagmus verteilten sich wie folgt: 2 verspürten *nur unregelmäßige, teilweise binoculär unkoordinierte* Augenbewegungen. 2 Vpn nahmen Nystagmus wahr, eine davon häufiger nur einen Augenzug *in Richtung der langsamen Phasen. 1 Versuchsperson spürte* nur diesen Zug in Richtung der langsamen Nystagmusphasen (vgl. Tab. 2). Man hatte den *Eindruck, daß Versuchspersonen von hoher Intelligenz ihre* Augenbewegungen leichter bemerkten.

Amplituden und *Intervallverteilung der* Nystagmusschläge änderten sich durch die Anaesthesie des Conjunctivalsackes nicht (Abb. 1).

With intact sensibility of conjunctiva and cornea there was no perception of eye movements in $^{7}/_{8}$ of the tests. In 17% of the tests the subjects felt a constant unilateral deviation of the eye balls, in 13% to the side of the slow nystagmus phase, and in 4% in the opposite direction. The subjects felt fast rhythmical eye movements in only 11% of the tests. These were insignificantly more often to the side of the fast phase of the vestibular nystagmus. Opening or closing the eyes did not influence these findings.

As soon as cornea and conjunctiva were anaesthetized there was no sensation of eye movement during vestibular nystagmus. It is concluded that corneal and conjunctival sensation plays an integral role in the perception of eye movement. Thus proprioceptors of the eye muscles are not sufficient for conscious sensation of eye movement.

These findings may correspond to the absence of a grouped neuronal discharge simultaneous with vestibular nystagmus observed on neurons of the cat's cortex in the absence of vision.

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Sehens keine dem vestibulären Nystagmus synchrone Entladungsrhythmik. Offenbar ist der Nystagmusrhythmus, d. h. die Einschaltung rascher Phasen in die vestibulären Augenbewegungen, eine vom Großhirn nur modulierend beeinflußte Hirnstammautomatik. Dem Cortex werden nicht die vestibulären Augenbewegungen als solche, sondern nur deren Ergebnisse, die durch veränderte *Blickstellungen* sichtbar gemachten Umweltausschnitte gemeldet (Kornhuber, 1962).

In Übereinstimmung damit ergab die vorliegende Untersuchung der Wahrnehmung von Augenbewegungen während des vestibulären Nystagmus, daß in rund zwei Drittel der 140 Einzelversuche der ersten Versuchsreihe und in rund drei Viertel der 40 vergleichbaren Versuche der zweiten Reihe, während des vestibulären Nystagmus bei Ausschluß des Sehens und intakter Sensibilität der Conjunctiva keinerlei Augenbewegung wahrgenommen wurde. Die in einem kleinen Teil der Versuche aufgetretene Wahrnehmung von Augenbewegungen während des vestibulären Nystagmus hängt, wie die Experimente mit Anaesthesie des Bindehautsackes (zweite Versuchsreihe) zeigten, von der *Sensibilität der Conjunctiva und Cornea* ab. Die Propriozeptoren der Augenmuskeln tragen zu dieser Wahrnehmung offenbar nichts bei. Die vestibuläre Erregung als solche führt zwar zu einer Wahrnehmung der Drehbeschleunigungsrichtung des Kopfes oder Körpers, aber nicht zur Wahrnehmung der vestibulären Augenbewegungen.

Bemerkenswert ist die schlechte Wahrnehmung der Augenbewegung in den raschen Nystagmusphasen. Rhythmische Augenbewegungen entsprechend dem vestibulären Nystagmus wurden nur in 10% der Versuche empfunden, und zwar teils in Richtung des Nystagmus, teils in Gegenrichtung *ohne bedeutsamen Unterschied. Wie schon erwähnt, wurden diese Augen*bewegungen nach Anaesthesie der Conjunctiva nicht mehr bemerkt. Eine statistisch bedeutsame richtige Wahrnehmung der Richtung der Augenbewegungen kam nur in Form eines Zuges zur Seite der langsamen Nystagmusphasen gelegentlich vor (24mal in Richtung der langsamen Nystagmusphasen, 6mal in Gegenrichtung bei 180 Versuchen). Auch hierbei handelt es sich nicht um vestibuläre oder um proprioceptive Meldungen aus den Augenmuskeln, sondern um eine Afferenz aus der Sensibilität der Conjunctiva und Cornea; nach Anaesthesie der Bindehaut verschwindet sie.

Unsere Ergebnisse bestätigen die Befunde von Brindley & Merton (1960), die durch passive Bewegung der Augen mit Pinzetten gewonnen wurden, und ergänzen sie *insofern, als auch vestibulär induzierte, binocular as*soziierte rasche und langsame Augenbewegungen wenig und bei Ausschaltung der Rezeptoren der Conjunctiva und Cornea gar nicht wahrgenommen werden.

SUMMARY

During rotatory tests carried out in a dark room 28 healthy persons were asked if they noticed any sensation of eye movements. Nystagmus was recorded electrically.

With intact sensibility of conjunctiva and cornea there was no perception of eye movements in $^2/_3$ of the tests In 17% of the tests the subjects felt a constant unilateral deviation of the eye balls, in 13% to the side of the slow nystagmus phase and in 4% in the opposite direction The subjects felt fast rhythmical eye movements in only 11% of the tests These were insignificantly more often to the side of the fast phase of the vestibular nystagmus Opening or closing the eyes did not influence these findings

As soon as cornea and conjunctiva were anaesthetized there was no sensation of eye movement during vestibular nystagmus It is concluded that corneal and conjunctival sensation plays an integral role in the perception of eye movement Thus proprioceptors of the eye muscles are not sufficient for conscious sensation of eye movement

These findings may correspond to the absence of a grouped neuronal discharge simultaneous with vestibular nystagmus observed on neurons of the cat's cortex in the absence of vision

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COMPARATIVE STUDIES OF AUDIOMETRIC BONE CONDUCTION

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The audiometric measurements of bone conduction were carried out on the two different places of the skull, i e on the mastoid process and on the frontal bone A comparison of the two methods of examination revealed that frontal bone conduction seems to give a better idea of the real state of the inner ear.

It has been well established that bone-conduction audiometry is very important mainly for the evaluation of the type of hearing impairment and therapeutic indications The mechanism of bone conduction is a complex phenomenon In physiological and pathological conditions it depends upon the mutual relations of five fundamental factors which were experimentally demonstrated by Barany and Bekesy They are

(1) the displacements in the canal due to relative movements of the mandible and the skull,
(2) the air-pressure in the tympanic cavity producing the movements of the stapes towards the inner ear,
(3) the displacement of the ossicular chain in relation to the walls of the tympanic cavity,
(4) the rhythmical compression of the labyrinth walls produced by the vibrations of the skull,
(5) the inertia of the ossicles in relation to the walls of the labyrinth

The influence of these five, and perhaps even more, factors can be changed in accordance with the preponderance of the osseous tympanic or the osseous-cochlear component of the bone conduction The question presents itself whether the way of the examination could influence the action of the above-mentioned factors in the perception of bone transmitted sounds

In searching for the best site during the examination of bone conduction, the bone vibrator was placed on the apex of the skull on the mastoid process, and on the frontal bone In audiometry the technique of the examination on the mastoid process has been generally accepted, but the method of examination with the bone vibrator or the tune-forks also has

adherents (Barany, 1938, Békésy, 1941, 1948, 1949, Becker, 1932, Hart & Naunton, 1961, Link & Zwislocki 1951)

Barany and Békésy recommend that technique because of the more homogeneous structure of the frontal bone The vibrator then causes more regular vibrations of the skull The tactile sensations which are produced by low frequencies are better differenciated from sound sensations Moreover, Link & Zwislocki (1951) believe that the measurements on the frontal bone reduce the influence of the middle ear mechanism on the bone-transmitted sounds

The purpose of this study was to find out which of the two examination methods is better in diagnosing the type of hearing impairment Furthermore it tries to ascertain the diagnostic value of the comparison between the audiometric thresholds of bone conduction which result from the measurements performed on the mastoid process and on the frontal bone

The investigations were carried out on the Polish audiometer "Elza", type AuG 60 The audiometer was previously calibrated by fixing the average threshold of bone conduction in young men with normal hearing Then the examination of bone conduction was performed in persons with normal hearing and in those with conductive, perceptive and mixed deafness These groups of patients included 20 persons each, totally 80 persons

The bone vibrator was put on the frontal bone and fixed close to the skull The opposite ear was masked with white noise of 50–70 db level Practically this location of the bone vibrator appeared to be better because of its greater stability on the skull, the headphones were not changed many times during the examination of both ears and it was very comfortable to perform the tests of Weber and Bing

For comparison the average audiometric thresholds for each group of patients were made according to the method used for the establishment of the standard threshold of bone conduction

The data obtained from this study are illustrated by a graphic diagram on the audiogram (Fig 1) This diagram shows the changes occurring in both examination methods in relation to the type of hearing losses and the frequency of sound stimulation

In normal hearing the closest coincidence of both curves is observed in the range of middle frequencies i e 1000 2000 c/s In three types of deafness the significant difference between two curves is observed at lower frequencies up to 1000 c/s This difference diminishes markedly beginning with the frequency of 1000 c/s in mixed and perceptive hearing impairments On the other hand it does not diminish in conductive deafness The frontal bone conduction thresholds then lie lower on the audiogram than the thresholds obtained on the mastoid process

These observations suggest that the location of the bone vibrator on the frontal bone, symmetrical to both ears, creates particular resonance condi-

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The influence of these five, and perhaps even more, factors can be changed in accordance with the preponderance of the osseous-tympanic or the osseous-cochlear component of the bone conduction. The question presents itself whether the way of the examination could influence the action of the above-mentioned factors in the perception of bone-transmitted sounds.

In searching for the best site during the examination of bone conduction, the bone vibrator was placed on the apex of the skull, on the mastoid process, and on the frontal bone. In audiometry the technique of the examination on the mastoid process has been generally accepted, but the method of examination with the bone vibrator or the tune-forks also has

air conduction curve below 60 db, which becomes distinctly lower at higher frequencies (*b*) the bone conduction curve situated above the air conduction curve but being lower than the normal one, (*c*) the descending course of the bone conduction curve at higher frequencies

The results of the examination of bone conduction in mixed deafness performed on the mastoid process and on the frontal bone are similar to those in normal hearing and in perceptive deafness It is probable that in more advanced hearing loss the importance of the osseous tympanic component of bone conduction is reduced and the osseous-cochlear component of bone conduction is of the greatest significance

The damage of the perceptive hearing organ does not influence the bone conduction in the two methods within the range of middle frequencies Evidently the resonance conditions in the middle ear are not changed here Other resonance conditions arise in the damaged middle ear, i e in conductive deafness The difference between bone conduction on the mastoid process and frontal bone conduction in the conductive type of hearing impairment probably results from the preponderance of inertia forces in cases of the lesions in the middle ear

As is known the osseous tympanic component causes the rise of the bone conduction threshold in the audiogram The lowering of the threshold of bone conduction measured on the frontal bone proves that in this method the middle ear is eliminated and that the osseous cochlear component of bone conduction is mainly investigated It appears that frontal bone conduction represents a more real threshold—one which reflects the actual state of the end hearing organ

CONCLUSIONS

1 Comparative audiometric investigations of bone conduction carried out on the mastoid process and on the frontal bone revealed the following (*a*) the mechanical forces of the middle ear are mostly responsible for the conduction of the middle frequencies (*b*) frontal bone conduction is less influenced by the mechanical forces of the middle ear and reflects more obviously the state of the inner ear

2 Frontal bone conduction is a valuable method of investigation and should be accepted in the routine examination of hearing

3 In diagnostically difficult cases referring mainly to mixed deafness the diagnosis of the type of hearing impairment can be made easier by the comparison of the two bone conduction thresholds obtained on the mastoid process and on the frontal bone

RÉSUMÉ

L'auteur a comparé la mesure de la conduction osseuse sur le mastoïde et sur le front La comparaison de ces deux méthodes des examinations a prouvé que la conduction osseuse examinée sur le front reflète plus distinctement l'état réel de l'oreille interne

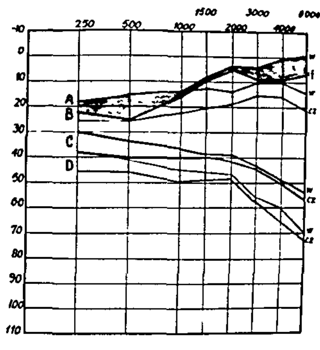


FIG 1 Average thresholds of bone conduction measured on the mastoid process and on the frontal bone *m* bone conduction threshold measured on the mastoid process, *f*, bone conduction threshold measured on the frontal bone (A) Both threshold curves of bone conduction in normal hearing (B) both threshold curves of bone conduction in conductive deafness, (C) both threshold curves of bone conduction in mixed deafness, (D) both threshold curves of bone conduction in perceptive deafness

tions for the middle frequencies, these are then reaching the inner ear with the same intensity as with the vibrator located in closer vicinity to the end hearing organ when the bone conduction is examined on the mastoid process

In the conductively impaired ear the conductive system of the middle ear is damaged, so the lack of coincidence in the two methods of examination—on the mastoid process and on the frontal bone—indicates that the state of the middle ear influences mostly the perception of the middle frequencies in bone-transmitted sounds The difference in the middle frequencies in bone conduction as measured on the mastoid process in comparison to the frontal bone conduction is the evidence that the conductive system is damaged The lack of difference proves that the middle ear is intact This observation is confirmed by the coincidence of the two bone-conduction thresholds in normal hearing and perceptive deafness The behaviour of bone conduction in the two examination methods in mixed deafness is yet to be explained Our data on the mean difference of bone conduction in mixed deafness were related to the cases with lesions of the middle ear with participation of the inner ear It was demonstrated by the following features of audiograms (*a*) the descending course of the

EFFERENT VESTIBULAR POTENTIALS BY CANALICULAR AND OTOLITHIC STIMULATIONS IN THE RABBIT

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By a physiological approach the presence of an efferent vestibular system in the rabbit is clearly demonstrated both in the case of canalicular and of otolithic stimulations This confirms the work of Schmidt and Henriksson on canalicular stimulations in the frog and is in accord with the report of Sala in the cat We were also able to demonstrate the presence of efferent potentials due to stimulation of the otoliths, which up to now, had not been demonstrated

Following the description by Cort (1918) of a vestibulocochlear anastomosing branch, and by Hardy (1934) of a cochleosaccular branch, no mention of this had been made in the literature until Rasmussen (1946, 1950) showed that Cort's bundle consists of fibers arising in the region of the superior olivary complex of the contralateral side, crossing in the olivary peduncle to join the vestibular portion of the VIII nerve The bundle leaves the inferior part of the vestibular nerve distal to the saccular ganglion as a discrete fascicle which enters the cochlea together with the cochlear nerve and forms the intraganglionic spiral bundle Fernandez (1951) has followed these fibers to the region of the internal hair cells

These fibers were then thought to be efferent, since they did not degenerate with the afferent fibers following severe acoustic trauma Based on the anatomical work of Rasmussen, the concept of an efferent cochlear system in the VIII nerve has been corroborated by several investigators who approached the problem from different angles from the anatomical point of view by Portmann & Portmann (1952), by means of electron microscopy by Wersäll (1956) and Engström (1958), physiologically by Galambos (1956) and Desmedt (1962), and biochemically by Schuknecht *et al* (1959)

While experiments of an anatomical, physiological, biochemical and electromicroscopical nature all seemed to corroborate the existence of an efferent cochlear system, it seemed logical to presume also an efferent vestibular system

Petroff (1955) first gave evidence of such a system He found that the fine fibers in the vestibular rami disappeared following midline transection in the floor of the fourth ventricle or by section of the VIII nerve.

ZUSAMMENFASSUNG

Es wurden audiometrische Untersuchungen von Knochenleitungen an zwei verschiedenen Schädelpunkten durchgeführt, nämlich am Mastoid und an der Stirn. Ein Vergleich dieser Untersuchungsmethoden zeigte, dass die an der Stirn untersuchte Knochenleitung den tatsächlichen Stand des Innenohres besser angab.

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similar to that described by McNally and Tait were able to demonstrate efferent labyrinthine impulses in the frog

Sala (1963) reported at the same time as Schmidt the presence of an efferent system in the cat by recording potentials from the vestibular nerve induced by electrical stimulation of the contralateral vestibular nuclei

These three reports seem to be the only studies reported to date of a physiological nature concerning the efferent system of the vestibular nerve Ledoux (1958) probably also demonstrated this system in reporting that the resting potential of a semi circular canal was decreased when the contra lateral canal was stimulated and though he does not comment on this it seems most probable that this is a result of inhibiting impulses propagated along efferent nerve fibers to the contralateral side

In our experiment we tried to demonstrate in mammals (rabbit) the presence of efferent vestibular potentials arising out of a physiological stimulation of the semi circular canals and utricular and saccular *otoliths*

METHOD

Surgical Approach

The experiments were carried out on rabbits of 2 to 3 kg with no apparent diseases or ear infections A total of 23 rabbits were used

The animals were fixed on a special board *in such a way* that the head could not move The first few animals were operated under general anaesthesia (nembutal) and no recordings were made until *the animals* were completely awake The waiting period being sometimes too long before we judged the animals to be sufficiently awake we then proceeded in all the subsequent animals to perform the operation under local anaesthesia (lidocaine 1% without *epinephrine*) using the minimum quantity possible to obtain good anaesthesia

We proceeded in the following manner After tracheotomy the *animal* was fixed in a prone position *and* the head fixed to the board Then a right or left labyrinthectomy was performed by using an anterior approach in the following *manner* A curved incision of about 2 to 2 5 cm was made anterior to the external ear *canal* and deepened to reach the anterior cartilaginous-osseous junction where the cartilage was sectioned from the bone The osseous *external* canal was *then freed* on the interior surface to the annulus tympanicus, and *exteriorly* to the squamal bone superiorly and anteriorly and to the mastoid posteriorly

After we had identified the stylo mastoid *foramen and* the facial nerve the external osseous canal was *removed* care being taken to preserve the facial nerve

With a dental drill the facial nerve was followed along the course of ... izontal segments

Fig. 1. Diagram of vestibular nerve and its branches showing pattern and distribution of vestibular efferent fibers (dashed lines). Efferent cochlear bundle is represented by dotted lines. From Gacek, 1960 (Fig. 190, p. 280).

Wersall (1956) made reference to such a system, while Rasmussen & Gacek (1958) and Gacek (1960) were able to give a direct demonstration of these fibers. Dohlman (1960), modifying slightly the technique used by Schuknecht *et al.* to demonstrate acetylcholinesterase activity in the cochlea, was able to demonstrate in the vestibular apparatus considerable acetylcholinesterase activity which seemed confined to the physiological function of the system of efferent fibers (in pigeons). Dohlman's experiment was further confirmed by Ireland & Farkashidy (1961) in mammals (with cats and guinea pigs).

Recently Rossi & Cortesina (1963) carried out a series of morphological and experimental investigations in the guinea pig studying the medulla oblongata in Nissl-stained sections, in sections submitted to Koelle and Friedenwald's reaction for acetylcholinesterase and in sections submitted to Cajal's reduced silver method of impregnation. From the study of retrograde cell degeneration after intracranial section of the VIII nerve and from the changes in acetylcholinesterase activity in the membranous labyrinth after section of the vestibular nerve, they were able to demonstrate the presence of five efferent bundles which connect the middle ear to the medulla.

The efferent vestibular system was also studied from a physiological angle. Schmidt (1963) and Henriksson (1963) using a surgical procedure

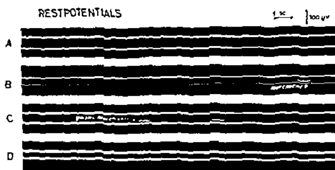


FIG 2 (A) Before labyrinthectomy (B) After labyrinthectomy (C) After decerebration (D) After contralateral labyrinthectomy

Nerve potentials of the superior branch of the vestibular nerve Before labyrinthectomy we note a continuous spontaneous discharge After unilateral labyrinthectomy the spontaneous discharge has disappeared *but movements of the rabbit can produce potentials* After decerebration passive movements of the rabbit do not evoke potentials

operation being under local anaesthesia, it would have been too traumatic to section the cervical nerves capable of influencing the vestibular pathways Therefore we believe that all possible extra labyrinthine stimuli *were not abolished and* could be partially provoked by neck movement or torsion However with the head fixed in such a way that it could not move *and the decerebrated rabbit tied* on the board there was no significant neck movement to elicit these potentials

All the experiments were conducted *in semidarkness with no light reflecting* at the rabbit's eye to eliminate the possibility of an optic stimulus inducing efferent potentials As can be seen in Fig 2 there exists *a continuous* spontaneous discharge before labyrinthectomy (A) which disappears following homolateral labyrinthectomy (B) Spontaneous or *provoked movements* of the limbs could still evoke efferent potentials After decerebration no efferent potentials could be elicited by passive movements of the limbs (C) After *contralateral labyrinthectomy* (D) as expected, there were no efferent potentials On rare occasions small potentials were recorded these were *attributed* to a cervical origin and were never present in post mortem controls

Stimuli *Two Types of Stimuli Used*

1 *Torsion swing*

This instrument was used *for pure rotational* stimulation of the semicircular canal *In a Faraday* cage the animal is placed on a torsion swing similar to that already described by van *Egmond* Groen and Jongkees With a stereotaxic manipulator the platinum *needle* is inserted into the superior branch of the vestibular nerve under direct *control* with a Zeiss

In order to perform this, the attic was exposed, the malleus and incus were removed and the facial nerve was then placed in the anterior part of the middle ear cavity.

We then clearly visualized the horizontal and vertical anterior canals which were opened with a polishing burr; the ampullae were exposed and the nerve to each ampulla identified The stapes and the bone above were removed and the utricular nerve was identified. The cochlea was destroyed

Afferent potentials can be recorded as expected (Ledoux, Ross, Löwenstein) In order to eliminate these, the nerves to the horizontal and vertical anterior canal and to the utriculus are sectioned and the latter are removed The sacculus and the posterior vertical canal were destroyed and removed

The head of the rabbit was fixed in such a position that the remaining contralateral horizontal canal was on an horizontal plane. A platinum electrode, completely isolated except for its distal 1 mm was placed on the superior branch of the vestibular nerve near the level where the utricular nerve separates from the branches going to the horizontal and vertical anterior canals The depth of the nerve and rabbit anatomy did not allow us to be positively certain whether we picked up potentials from only one branch so that we decided to pick them up on the whole superior branch rather than on one of its three endings One drop of lidocaine 1% was placed on the cut end of the nerve to eliminate potentials that could arise from it

Recordings of efferent potentials were then made with various stimuli, after which a decerebration at the level of C 2 was performed to eliminate an important number of extra labyrinthine proprioceptive receptors After again recording efferent potentials with the same stimuli as before and in the same conditions, a contralateral labyrinthectomy was performed and recording repeated The animals were then killed and the tests repeated to eliminate the possibility of artefacts

Recordings and Stimuli

Recordings were made with a Tektronix oscilloscope type 502, after amplification with a type E preamplifier

Before studying the effect of different stimuli, a study of rest potentials and extra-labyrinthine factors must be considered In every animal, before stimulus was applied, rest potentials were studied in every condition before labyrinthectomy, after homolateral labyrinthectomy after contralateral labyrinthectomy, after decerebration and after death

A factor of great importance was *the study of extra-labyrinthine stimuli* Before decerebration any spontaneous or provoked movement of the limbs or the body of the rabbit produced efferent potentials These potentials were almost abolished by decerebration at the level of C 2 We could not completely abolish extra labyrinthine potentials due to the fact that, the

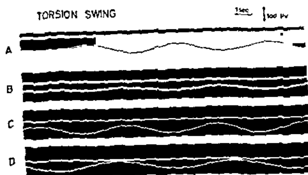


Fig. 5. (A) After unilateral labyrinthectomy. (B) After decerebration. (C) After contralateral labyrinthectomy. (D) After death. Upper lines: recording of potentials. lower lines: movements of the swing.

Efferent potentials appear in both directions in A and B with torsion swing induced canicular stimuli and are abolished following a contralateral labyrinthectomy and using the same stimuli as in A and B. The post mortem control which was always done in the same manner shows no recording which could be attributed to artefacts.

RESULTS

Rest Potentials

Before labyrinthectomy it was observed that after a slight exposure of the vestibular nerve rest potentials could be recorded much in the same way as in the frog as already described by Ross, Löwenstein, and Ledoux.

After labyrinthectomy there are no spontaneous rest potentials. These can, however, be elicited by spontaneous or provoked movements of the limbs or body of the rabbit. Noise induced by hand-clapping or metallic

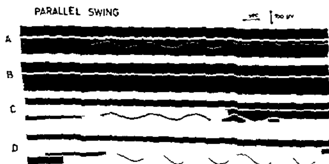


Fig. 6. (A) After unilateral labyrinthectomy. (B) After decerebration. (C) After contralateral labyrinthectomy. (D) After death. Upper lines: recording of potentials. lower lines: movements of the swing.

Efferent potentials are evoked by the parallel swing producing, by linear acceleration, a stimulation of the otoliths in A and B. These are abolished following a contralateral labyrinthectomy. They are absent in the post mortem control.

TORSION SWING

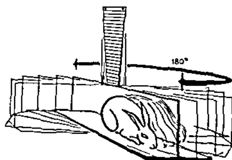


FIG 3 Schematic drawing showing the principle of the torsion swing From a resting position the swing is first turned 90° to the left and the following turns alternate from the right to the left in a decreasing amplitude with each turn

microscope After having recorded rest potentials, we stimulated the contralateral horizontal canal with a series of turns of decreasing amplitude

2 *Parallel swing*

The second stimulus is given by a parallel swing On this swing the animal is subjected to a pure linear acceleration which stimulates the otoliths Following the torsion swing the animal is placed on a parallel swing and the platinum electrode again placed on the superior branch of the vestibular nerve with the stereotaxic manipulator under control with a Zeiss microscope Again recordings are made with a single or a series of movements, with the animal being on the swing first in a lengthwise position, thereafter in a sideways position

PARALLEL SWING

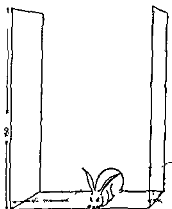


FIG 4 Schematic drawing showing the principle of stimulation with the parallel swing The results are identical whether the rabbit is in a sideways position as above or in a lengthwise position

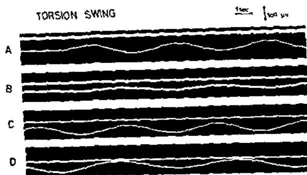


Fig. 5. (A) After unilateral labyrinthectomy. (B) After decerebration. (C) After contralateral labyrinthectomy. (D) After death. Upper lines: recording of potentials; lower lines: movements of the swing.

Efferent potentials appear in both directions in A and B with torsion swing induced canicular stimuli and are abolished following a contralateral labyrinthectomy and using the same stimuli as in A and B. The post mortem control, which was always done in the same manner, shows no recording which could be attributed to artefacts.

RESULTS

Rest Potentials

Before labyrinthectomy it was observed that after a slight exposure of the vestibular nerve rest potentials could be recorded much in the same way as *in the frog* as already described by Ross, Löwenstein and Ledoux.

After labyrinthectomy there are no spontaneous rest potentials. These can, however, be elicited by spontaneous or provoked *movements* of the limbs or body of the rabbit. Noise induced by hand clapping or metallic

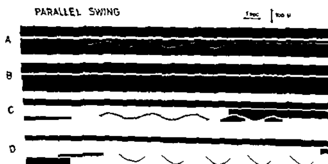


Fig. 6. (A) After *unilateral* labyrinthectomy. (B) After decerebration. (C) *After* contralateral labyrinthectomy. (D) *After* death. Upper lines: recording of *potentials*; lower lines: movements of the *swing*.

Efferent potentials are evoked by the parallel *swing* producing by linear acceleration a stimulation of the otoliths in A and B. These are abolished following a contralateral labyrinthectomy. They are absent in the post mortem *control*.

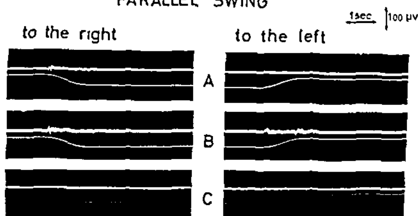


FIG 7 (A) After unilateral labyrinthectomy (B) After decerebration (C) After contralateral labyrinthectomy Upper lines, recording of potentials, lower lines movements of the swing

Single movements of the parallel swing Either direction clearly show the relation between the stimulus and the response

clicks did not provoke potentials unless the animal moved This could be better corroborated after decerebration, then the animal did not move at all

Torsion swing

With a series of movements or by single turn potentials could be elicited in both directions While our study is made on a qualitative rather than quantitative response it seems that the ampullopetal rather than ampullofugal stimulation of the contralateral horizontal canal provokes a greater response The same results were obtained before and after decerebration Following contralateral labyrinthectomy the potentials evoked by torsion swing movement were almost totally abolished, the occasional one recorded being possibly of optokinetic or cervical origin After the animal is killed, a control is made of the torsion swing to determine whether there are artefacts in our technique The post-mortem control showed no potentials These results were obtained in 21 out of the 23 rabbits submitted to the torsion swing stimulus, no response being obtained in 2 rabbits

Parallel swing

For the recording of potentials induced by the parallel swing the platinum is put as close as possible to the end of the utricular nerve By a single movement or by a series of movements potentials could be evoked in both directions whether the animal was placed on the swing in a lengthwise or sideways position These results were obtained in 15 of the 16 rabbits which were submitted to the parallel swing stimulation, only 1 rabbit giving no response

Efferent potentials from otolithic stimulations were not recorded by

other authors. Yet we regularly obtained efferent potentials using a parallel swing stimulation. Contrary to Schmidt's technique, where changes of position were used as an otolithic stimulus, we used a parallel swing. The reason of our choice was that our manipulation and our fixation apparatus did not allow us an easy control of the electrode needle under microscopic control in certain positions.

Another important reason for using the parallel swing stimulus is that it is constantly changing its direction (whereas positional stimulus is always in the same direction) and therefore does not lead to adaptation or fatigue.

As with the torsion swing stimulus these potentials were abolished after a contralateral labyrinthectomy and on post mortem recordings.

ZUSAMMENFASSUNG

Die Anwesenheit eines efferenten Vestibularsystems beim Kaninchen wurde durch physiologische Reizung des horizontalen Kanals und des Otolithenorgans deutlich erwiesen. Die von Schmidt und Henriksson beim Frosch über die Stimulation der Bogengänge gemachten Experimente werden bestätigt. Ebenso stimmen unsere Experimente mit der Arbeit von Sala über der Katze überein.

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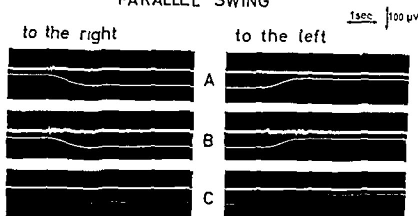


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EFFECT OF TYMPANIC MUSCLE ACTIVITY ON MOVEMENT OF THE EARDRUM, ACOUSTIC IMPEDANCE AND COCHLEAR MICROPHONICS[1]

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The functions of the tympanic muscles were studied in anesthetized cats and rabbits. The change in air pressure produced in the closed external auditory meatus and in the acoustic impedance near the ear drum was recorded during (1) independent contraction of the two tympanic muscles and during (2) contraction of the two muscles together. The change in cochlear microphonics following contraction of the tympanic muscles was also studied. As expected, it was found that a contraction of the tensor tympani always produced a negative pressure change in the meatus indicating an inward movement of the eardrum. A contraction of the stapedius muscle produced no change or considerably smaller pressure change which could be either positive or negative. It was further found that simultaneous contraction of the two muscles produced a negative change in the air pressure the magnitude of which was smaller than that produced by the tensor tympani alone. Independent contraction of the stapedius and the tensor tympani muscles produced a change within the same range of magnitude in the acoustic impedance as well as in the cochlear microphonics potential. The effect on the acoustic impedance and the cochlear microphonics of both muscles acting together was greater than that produced by either of the muscles when contracting alone.

The results of the experiments indicate that a contraction of the stapedius muscle counteracts the effect of the tensor tympani on the movement of the eardrum and further that the combined action of the two muscles on acoustic impedance and cochlear microphonics is greater than that of the two muscles acting alone.

INTRODUCTION

The anatomical arrangement of the middle ear muscles is such that contraction of the tensor tympani muscle pulls the manubrium of the malleus inward and contraction of the stapedius muscle moves the stapes

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EXPERIMENTAL PROCEDURE

Young cats and rabbits (ca 2.5 kg) were used in all experiments. The rabbits were anesthetized with urethane (1.5 gr/kg *i.v.*) or pentobarbital sodium (Nembutal, Abbott, for veterinary use 0.7 ml/kg *i.v.*) while only Nembutal (0.7 ml/kg *i.p.*) was administered routinely to the cats. In some cases atrophine sulphate (3 mg/kg *i.m.* in the rabbits and 0.3 mg/kg *i.m.* in the cats, every two hours) was administered in order to reduce salivation. With the aid of a binocular operating microscope (Zeiss Epitekno-skop) the middle ear cavity was exposed and when cats were used the bony septum was visualized and removed. The outer ear was resected leaving about 5 mm of cartilageous ear canal intact and a metal tube 10 mm long and 4.5 mm in diameter was inserted into the external auditory meatus and firmly secured to the remaining ear canal. The various instruments described below and used to measure air pressure in the ear canal and acoustic impedance at the eardrum were connected to the exposed end of the metal tube.

Bipolar electrodes were applied near the origin of the tensor tympani as well as on or near the tendon of the stapedius muscle and the muscles were stimulated independently with single or repetitive rectangular pulses of 0.1 msec duration.

In order to prevent the influence of possible stimulus spread between the two muscles when they were stimulated simultaneously the stimuli were delivered with a small time difference (1 msec).

The change in air pressure produced by middle ear muscle activity was measured with a condenser microphone (Bruel & Kjær type 4134) and an electromanometer (Elema type EMT 573) in order to study the full range of pressure change. The condenser microphone had a high pass frequency characteristic with a cut off frequency of about 17 cps and below this frequency the response decayed approximately 12 db/octave. Thus the slow pressure variations were attenuated and the fast changes uniformly reproduced. The electromanometer however had a low pass frequency characteristic and an upper cut off frequency of 70 cps resulting in faithful reproduction of the slow changes in air pressure and attenuation of the fast changes.

The equivalent volume of the electromanometer used was about 20 cc. The displacement at the eardrum (ΔV) is equal to $\frac{\Delta P\, V}{P}$ where ΔP is the measured pressure change, V the total volume (20 cc) and P the atmospheric pressure.

The acoustic impedance changes were measured at a frequency of 800 cps in the same manner as described previously (Møller 1961).

The cochlear microphonic potential was recorded near the round window, amplified and filtered with band pass filters with a characteristic equal to [illegible] used in the apparatus for measuring the impedance

These displacements of the ossicles result in reduced mobility of the ossicular chain and a simultaneous movement of the eardrum This movement of the eardrum may be utilized to study acoustic middle ear reflexes in animal experiments as shown by Kato (1913)

If the external ear canal is sealed air tight, movements of the eardrum produced by contraction of the middle ear muscles result in measurable changes in the air pressure within the sealed canal This phenomenon has been used in studies of the middle ear muscle contraction elicited by contralateral sound stimulation (Mangold, 1913; Kobrak, 1957, Mendelson, 1957; Terkildsen, 1957, Holst, Ingelstedt & Örtengren, 1963) The direction of the eardrum movement, indicated by the change in air pressure in the ear canal has also been used to determine which of the two muscles is involved in the acoustic reflex (Terkildsen, 1960 *a*, Weiss *et al*, 1963)

When the tensor tympani contracts, the eardrum always moves inward producing a negative pressure in the sealed ear canal When the stapedius muscle contracts the eardrum movement and resultant pressure change are more difficult to predict due to the complex arrangement of the stapes and its displacement following stapedius muscle contraction The stapedius muscle pulls the stapes in a direction which is almost perpendicular to the outward–inward movement of the stapes foot plate which corresponds to a similar movement of the eardrum Since contraction of the stapedius muscle also causes a gliding motion in the incudostapedial joint it may also produce a movement of the incus The resultant movement of the eardrum will then depend upon the exact direction of the stapes displacement

The change in mobility of the middle ear system caused by contraction of the tensor tympani and the stapedius muscles results in a change in the acoustic impedance at the eardrum (Geffcken, 1934) and has been used in studies of the middle ear muscle activity in man (Metz, 1951, Jepsen, 1955, Møller, 1958, 1962, Terkildsen, 1960 *b*, Klockhoff, 1961, Djupesland, 1962)

Finally, contraction of the middle ear muscles may alter sound transmission through the middle ear which can be measured as a change in the cochlear microphonic potential (Hallpike, 1935 Wiggers 1937, Wever & Vernon, 1955, Galambos & Rupert 1959, Simmons, 1959) Thus it is possible to utilize the change in the cochlear potential as a further measure of muscle activity

It is not clear, however, from the previous investigations whether the two muscles act as antagonists or as synergists with respect to the displacement of the eardrum, the cochlear microphonics and the acoustic impedance

In this paper results are reported on the individual and combined effects of contractions of the middle ear muscles in cats and rabbits on the *movement of the eardrum*, on the *acoustic impedance* and on the *cochlear microphonics*

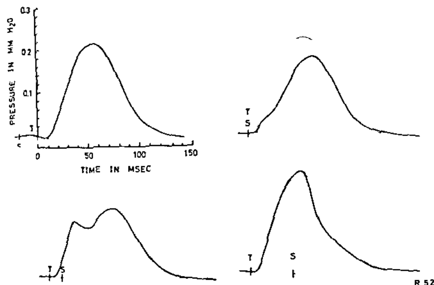


Fig. 2. Tracings of recordings of the air pressure in the sealed ear canal in a rabbit. The dotted line represents the air pressure during contraction of the tensor tympani muscle, the dashes the air pressure during stapedius muscle contraction and the solid line represents the change in air pressure during contraction of both muscles. The time for stimulation of the muscles is marked with vertical lines on the curves. Upward deflection represents negative pressure.

made with the condenser microphone because of its attenuation of low frequencies.

Records 1 A and D were taken during contraction of the tensor muscle and records B and E were obtained during stapedius contraction. The change in air pressure during simultaneous contraction of both muscles is seen in C and F. Upward deflection represents a change in negative direction.

As expected, a contraction of the tensor tympani muscle produced a negative pressure change in the ear canal (Fig. 1, A and D). A contraction of the stapedius muscle, on the other hand, produces either a negative or a positive pressure change in the ear canal. The pressure change produced by a contraction of the stapedius muscle was, however, much smaller than that produced by a contraction of the tensor tympani muscle (see Fig. 1, B and E), although the stapedius contraction produced a substantial displacement of the stapes as judged by visual inspection. It should be further mentioned that contraction of the stapedius muscle also was observed to produce a diphasic change in the air pressure showing that the eardrum was first moved in one direction and later during the contraction, in the opposite direction. When the stapedius muscle was activated simultaneously with the tensor tympani the effect of the tensor contraction was diminished (Fig. 1, C and F) independent of the direction of the eardrum movement induced by the stapedius contraction.

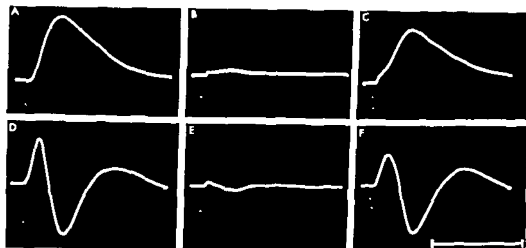


Fig. 1. Change in the air pressure in the sealed ear canal during twitch contraction of the tympanic muscles in a cat. *A*, *B* and *C* are recordings made with the electromanometer and *D*, *E* and *F* are recordings made with the condenser microphone. *A* and *D* show change in air pressure during contraction of the tensor tympani, *B* and *E* during contraction of the stapedius muscle and *C* and *F* show the change in air pressure during simultaneously contraction of both muscles. The dots indicate application of the stimulus. Time calibration is 100 msec. Upward deflection represents negative pressure.

change. Since the muscles were stimulated electrically with up to 10 volts and the recorded cochlear microphonic potential was in the order of 10 microvolts the following precautions were taken to avoid the distorting effect of the artefact on the recorded cochlear microphonics. Because of the smoothing effect of the band-pass filters used to filter the cochlear microphonics the stimulus artefact spreads out in time and obscures the change in the cochlear microphonics caused by contraction of the muscles. In order to prevent the artefact from entering the filter a gate was inserted in the amplifier before the filter. This gate was closed during stimulation and opened before the start of the muscle contraction thus avoiding the interference of the stimulus artefact with the cochlear microphonics during the time when the muscles were active.

In order to eliminate the possibility of contraction of muscles other than the tensor tympani and the stapedius due to stimulation of the trigeminal and facial nerves some of the animals were curarized (Flaxedil 0.2 ml/kg i.v.).

RESULTS

Change in air pressure

The records in Fig. 1 show changes in the air pressure in the sealed auditory canal in a cat recorded with the electromanometer (A, B and C) and with the condenser microphone (D, E and F). The electromanometer reproduces slow variations in air pressure whereas the condenser microphone records only the fast change in air pressure. Thus, interference from slow variations in the air pressure is eliminated in the recordings

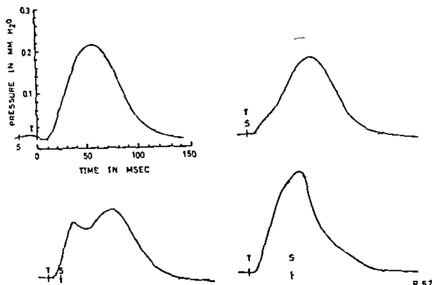


Fig 2 Tracings of recordings of the air pressure in the sealed ear canal in a rabbit The dotted line represents the air pressure during contraction of the tensor tympani muscle the dashes the air pressure during stapedius muscle contraction and the solid line represents the change in air pressure during contraction of both muscles The time for stimulation of the muscles is marked with vertical lines on the curves Upward deflection represents negative pressure

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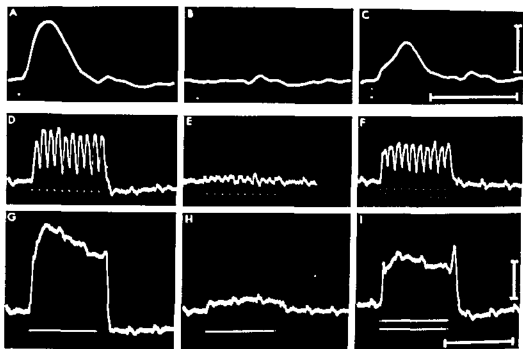


FIG 3 Change in air pressure in the sealed ear canal during single (*A*, *B* and *C*) and during repetitive (*D*–*I*) stimulation in a rabbit *A*, *D* and *G* represents contraction of the tensor tympani muscle, *B* *E* and *H* stapedius contraction and *C*, *F* and *I* simultaneously contraction of both muscles Recordings of the stimulus is seen below Calibration is 100 msec and 0 1 mm H_2O for the twitch contraction and 500 msec and 0 2 mm H_2O for the repetitive stimulation Upward deflection represents negative pressure

Fig 2 illustrates the effects on the air pressure produced by stimulation of one muscle succeeded by activation of the other one at varying time intervals The dotted lines represent the air pressure during contraction of the tensor tympani muscle alone and the dashed lines show the air pressure during stapedius muscle contraction The solid lines show the air pressure during contraction of both muscles (stimulation marked with the vertical lines T and S on the curves) The results indicate that a contraction of the stapedius muscle reduces the pressure change produced by a tensor contraction, although a stapedius contraction alone does not produce any significant pressure change in the ear canal

The recordings in Fig 3 were made during single (A, B and C) and repetitive (D–I) stimulation of the tympanic muscles independently and simultaneously in a rabbit The results during twitch contraction as well as during repetitive stimulation show that the change in air pressure is less when both muscles contract simultaneously (C, F and I) than when the tensor tympani muscle contracts alone (A, D and G) although the stapedius muscle contraction alone does not produce any significant change in the air pressure (B, E and H) In addition, a comparison of Fig 1, 2 and 3 indicates that the results from experiments on cats and rabbits are the same



Fig 4 Change in air pressure (upper curves) recorded simultaneously with the change in acoustic impedance in a cat curarized with Flaxedil *A* represents contraction of the tensor tympani muscle, *B* the stapedius muscle and *C* simultaneously contraction of both muscles Calibrations 100 msec and 0 2 mm H_2O

Acoustic impedance change

As mentioned above the change in air pressure in the ear canal is a measure of the displacement of the eardrum while the change in the acoustic impedance may be used to indicate the change in mobility of the middle ear measured at the eardrum In order to investigate the relation between the change in air pressure and the change in acoustic impedance these changes were recorded simultaneously during contraction of the middle ear muscles

Simultaneous recordings of changes in the acoustic impedance and the air pressure in the ear canal in a cat during contraction of the middle ear muscles are shown in Fig 4 The upper curves show the air pressure recorded with the electromanometer and the lower curves show the changes in the impedance recorded with a 800 cps signal

It is seen from Fig 4 B that a contraction of the stapedius muscle produces a substantial impedance change The change in air pressure (Fig 4 B) however, is much smaller than that produced by the tensor muscle (Fig 4 A) and its direction is unpredictable The tensor tympani muscle on the other hand produces a change in air pressure as well as a change in the acoustic impedance as can be seen from Fig 4 A Figure 4 C indicates that the impedance change is larger when both muscles contract simultaneously than it is when the muscles contract independently

Change in cochlear microphonics

A contraction of the middle ear muscles also causes a change in the transmission properties of the middle ear which can be measured as a change in the cochlear microphonics recorded near the round window

Records 5, A, B and C show the changes in the acoustic impedance and the cochlear microphonics potential near the round window, recorded simultaneously during contraction of the tensor tympani muscle (A), the stapedius muscle (B) and both muscles together (C) The changes in the

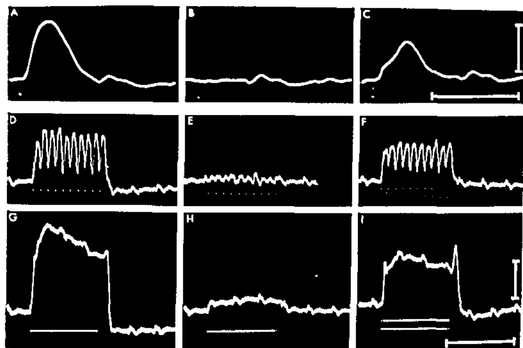


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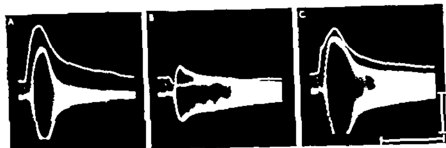


FIG 4 Change in air pressure (upper curves) recorded simultaneously with the change in acoustic impedance in a cat curarized with Flaxedil *A* represents contraction of the tensor tympani muscle *B* the stapedius muscle and *C* simultaneously contraction of both muscles Calibrations 100 msec and 0 2 mm H_2O

Acoustic impedance change

As mentioned above the change in air pressure in the ear canal is a measure of the displacement of the eardrum while the change in the acoustic impedance may be used to indicate the change in mobility of the middle ear measured at the eardrum In order to investigate the relation between the change in air pressure and the change in acoustic impedance these changes were recorded simultaneously during contraction of the middle ear muscles

Simultaneous recordings of changes in the acoustic impedance and the air pressure in the ear canal in a cat during contraction of the middle ear muscles are shown in Fig 4 The upper curves show the air pressure recorded with the electromanometer and the lower curves show the changes in the impedance recorded with a 800 cps signal

It is seen from Fig 4 B that a contraction of the stapedius muscle produces a substantial impedance change The change in air pressure (Fig 4 B) however is much smaller than that produced by the tensor muscle (Fig 4 A) and its direction is unpredictable The tensor tympani muscle on the other hand produces a change in air pressure as well as a change in the acoustic impedance as can be seen from Fig 4 A Figure 4 C indicates that the impedance change is larger when both muscles contract simultaneously than it is when the muscles contract independently

Change in cochlear microphonics

A contraction of the middle ear muscles also causes a change in the transmission properties of the middle ear which can be measured as a change in the cochlear microphonics recorded near the round window

Records 5 A B and C show the changes in the acoustic impedance and the cochlear microphonics potential near the round window, recorded simultaneously during contraction of the tensor tympani muscle (A) the stapedius muscle (B) and both muscles together (C) The changes in the

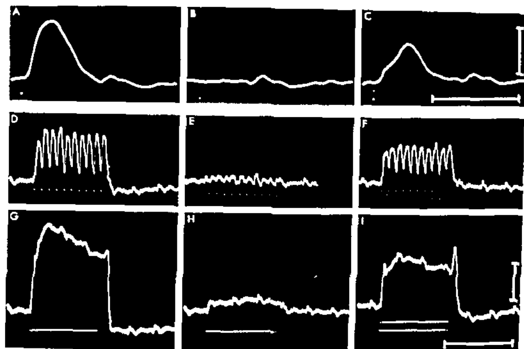


Fig 3 Change in air pressure in the sealed ear canal during single (A, B and C) and during repetitive (*D–I*) stimulation in a rabbit *A, D* and *G* represents contraction of the tensor tympani muscle, *B, E* and *H* stapedius contraction and *C, F* and *I* simultane*ously contraction of both muscles Recordings of the stimulus is seen below Calibration* is 100 msec and 0 1 mm H_2O for the twitch contraction and 500 msec and 0 2 mm H_2O for the repetitive stimulation Upward deflection represents negative pressure

Fig 2 illustrates the effects on the air pressure produced by stimulation of one muscle succeeded by activation of the other one at varying time intervals The dotted lines represent the air pressure during contraction of the tensor tympani muscle alone and the dashed lines show the air pressure during stapedius muscle contraction The solid lines show the *air pressure during contraction of both muscles (stimulation marked with* the vertical lines T and S on the curves) The results indicate that a contraction of the stapedius muscle reduces the pressure change produced by a tensor contraction, although a stapedius contraction alone does not produce any significant pressure change in the ear canal

The recordings in Fig 3 were made during single (A, B and C) and repetitive (D I) stimulation of the tympanic muscles independently and simultaneously in a rabbit The results during twitch contraction as well as during repetitive stimulation show that the change in air pressure is less when both muscles contract simultaneously (C, F and I) than when *the tensor tympani muscle contracts alone* (A, D and G) although the stapedius muscle contraction alone does not produce any significant change in the air pressure (B, E and H) In addition, a comparison of Fig 1, 2 and 3 indicates that the results from experiments on cats and rabbits are the same

to humans it seems difficult to make any conclusions from a negative pressure change since according to these results a negative pressure change may be produced by a contraction of (1) the tensor tympani muscle (2) the stapedius muscle or (3) both A positive pressure change, however, can only be caused by a stapedius muscle contraction

ZUSAMMENFASSUNG

Zur Untersuchung der Funktionsweise der Mittelohrmuskeln wurde an narkotisierten Katzen und Kaninchen die Kontraktion der beiden Muskeln durch elektrischen Reiz ausgelost und die dabei auftretenden Anderungen des statischen Luftdrucks in dem abgeschlossenen ausseren Gehorgang und der akustischen Impedanz nahe am Trommelfell aufgezeichnet und zwar einmal bei Kontraktion eines der beiden Muskeln und zum andern bei gleichzeitiger Kontraktionsauslosung beider Muskeln Im Zusammenhang damit wurden des weiteren auch die infolge der Kontraktion auftretenden Anderungen der Cochlear Mikrophonpotentiale untersucht Wie zu erwarten war bewirkte eine Kontraktion des *m tensor tympani* immer eine negative Druckanderung im Gehorgang woraus auf eine Verschiebung des Trommelfells ins Mittelohr *hinein zu schliessen ist* Eine Kontraktion des *m stapedius* dagegen zeigte entweder gar keine Anderung des statischen Drucks oder aber eine betrachlich kleinere Anderung als im Falle des *m tensor tympani* die sowohl positiv wie negativ sein konnte Eine gleichzeitige Kontraktionsauslosung beider Muskeln bewirkte eine negative Druckanderung die aber kleiner war als alleiniger Kontraktion des *m tensor tympani* Die Kontraktion des *m stapedius* zeigt auch hinsichtlich der Verschiebung des Trommelfells einen hemmenden Effekt auf die Einwirkung des *m tensor tympani* Bei Kontraktion jedes der beiden Muskeln fur sich war die Anderung der akustischen Impedanz in beiden Fallen von der gleichen Grossenordnung und ebenso auch die der Cochlear Mikrophonpotentiale Gleichzeitige Auslosung der Kontraktion der beiden Muskeln bewirkte *dagegen eine grossere* Anderung sowohl der akustischen Impedanz wie auch der Cochlear Mikrophonpotentiale als bei Kontraktion jedes Muskels einzeln fur sich

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Fig. 5. Upper curves: Change in acoustic impedance at 800 cps recorded simultaneously with the cochlear microphonics (lower curves) in a cat. A represents contraction of the *tensor tympani muscle*, *B* the stapedius muscle and *C* simultaneously contraction of both muscles. Time calibration: 100 msec.

acoustic impedance and the cochlear microphonics were both measured at a frequency of 800 cps. It is seen that the changes in impedance and in cochlear microphonics have the same time course. Stimulation of either muscle independently produced a change in the cochlear microphonic potential which was within the same range. The combined action of the two muscles is followed by a larger change in impedance as well as in cochlear microphonics.

DISCUSSION

The results of the present investigation indicate that the stapedius muscle does not produce any significant *movement of the eardrum* compared to that produced by the tensor tympani muscle and that a stapedius muscle contraction counteracts the movement produced by a tensor contraction. When the *mobility* and *transmission property* of the middle ear are considered the middle ear muscles act as synergists and the effect of a contraction of each of the two muscles, although not necessarily equal, is of the same order of magnitude.

The results obtained in *cats* and *rabbits* are identical. There is good reason to believe that the results may be applicable to the human ear since the anatomy is similar to that of the two animals. For the purpose of recording the net effect of the activity of the middle ear muscles measurement of the acoustic impedance change is considered to be superior to measurement of the change in air pressure in the ear canal since a contraction of the stapedius muscle does not necessarily produce any change in the air pressure whereas it always produces an impedance change of measurable magnitude.

The change in air pressure in the auditory canal has been used in investigations of human ear muscle activity in order to find out which of the two muscles are involved in the acoustic reflex (Terkildsen, 1960 *a*, Weiss *et al.*, 1963). If the results of the present experiments are applicable

UPPER AIRWAY RESISTANCE IN NORMAL MAN DURING MOUTH BREATHING[1]

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Upper airway resistance was measured as the relationship between pressure drop across, and flow through, the upper airway in 10 men and 8 women. The pressure drop was measured by a direct method after puncture of the cricothyroid membrane. The relationship between pressure difference and flow was curvilinear during both inspiration and expiration and for both resting ventilation and hyperventilation, this indicates the presence of turbulent flow. All curves could be represented by second degree polynomials.

Resting ventilation resistance tended to be higher than hyperventilation resistance, this was especially apparent during expiration and for women. The mean upper airway resistance at a flow rate of 0.5 l/sec was 1.0 cm H_2O/l/sec at rest. During hyperventilation it was 0.8 and 1.2 cm H_2O/l/sec for flow rates of 0.5 and 1.0 l/sec, respectively. The upper airway resistance was approximately one half of the total airway resistance.

The mechanical work performed in moving air through the upper airway was determined as the product of the ventilated volume and pressure drop across this segment of the tract. During resting ventilation it was 0.008 and 0.006 kpm/l of V_E for men and women, respectively.

INTRODUCTION

During inspiration the thoracic volume increases and the alveolar pressure is lowered below atmospheric. During expiration a positive pressure difference is set up. These pressure differences, which cause air to flow into and out of the alveoli, are not levelled out instantly owing to the resistance to the air flow presented by the nasopharynx, larynx and bronchial tree. The sum of these resistances is referred to as the airway resistance and is defined as the relationship between the pressure difference between the alveoli and the atmosphere, i.e. the driving pressure (P), and the resulting airflow ($\dot{V}$). The magnitude of the driving pressure is dependent

[1] This study has been supported by grants from Karolinska Institutet and the Swedish National Association against Heart and Chest Diseases.

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Resting ventilation resistance tended to be higher than hyperventilation resistance this was especially apparent during expiration and for women The mean upper airway resistance at a flow rate of 0 5 l/sec was 1 6 cm H_2O l sec at rest During hyperventilation it was 0 8 and 1 . cm H_2O l sec for flow rates of 0 5 and 1 0 l/sec respectively The upper airway resistance was approximately one half of the total airway resistance

The mechanical work performed in moving air through the upper airway was determined as the product of the ventilated volume and pressure drop across this segment of the tract During resting ventilation it was 0 008 and 0 006 kpm l of V_E for men and women respectively

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than during resting ventilation for the same moderate flow This applied to both inspiration and expiration (Hyatt & Wilcox, 1961)

The cumulative product of the intrathoracic pressure and ventilated air volume at each instant of the respiratory cycle constitutes a measure of the mechanical work that has to be performed to ventilate the lungs (Rohrer, 1915, Rossier, Bühlmann & Wiesinger, 1958, Comroe *et al*, 1962) The mechanical work required to force air through the upper respiratory tract may be determined by measuring simultaneously the pressure difference across the upper airway and the respiratory volume

The aim of the present study was to examine the pressure-flow and pressure-volume relationships in the normal upper airway, defined here as the segment of the respiratory tract extending from the oral aperture to the subglottic space This study was intended to form a basis for an investigation of upper airway resistance under pathologic conditions

MATERIAL

The study was performed on 18 subjects (10 men and 8 women), recruited among patients at the Department of Otolaryngology of the Karolinska Sjukhuset and among student nurses The mean ages were 50 6 (range 32–73) and 33 3 (range 19–62) years for men and women, respectively All had been examined by indirect laryngoscopy and found to be normal One woman was excluded from the hyperventilation study owing to a technical mishap For the same reason the determination of respiratory mechanical work was omitted for one man

METHOD

The measurement of upper airway resistance requires simultaneous recording of volume flow through, and pressure gradient across, this part of the respiratory tract

Apparatus

The subglottic lateral pressure was measured after puncture of the cricothyroid membrane with a blunt needle (41 mm in length, 1 0 and 1 5 mm in internal and external diameters, respectively) provided with a sharp mandrin[1] The needle was mounted on a plate that could be pushed down against the skin after the puncture and kept in place by means of a screw (Fig 1) The pressure at the mouth was measured after puncture of the mouthpiece between the subject and the flow-meter This needle was identical with the former one The difference in lateral pressure between the subglottic space and the mouthpiece was measured with an inductance differential manometer[2] connected to the needles with short Teflon tubes

[1] AB Kifa Solna Sweden

[2] Pneumomanometer, model FMT 573 Flema AB Solna, Sweden

on the friction within the air stream and between this and the walls of the conducting system, and on the flow rate of the air. Rohrer (1915) expressed the driving pressure by the equation:

$$P = K_1\dot{V} + K_2\dot{V}^2,$$

where the first and second degree terms represent laminar and turbulent flow, respectively. The constant K_1 is proportional to the viscosity of the air and K_2 to its density This relationship is valid provided that the dimensions of the air-conducting system and the properties of the air remain constant throughout the respiratory cycle

A considerable part of the total airway resistance is due to the constriction of the respiratory tract in the larynx (von Neergaard & Wirz, 1927, Vuilleumier, 1944; Hyatt & Wilcox, 1961) According to Rohrer (1915) nine-tenths of the resistance due to turbulent flow is set up in the upper airways, the larynx alone contributes two-thirds of it; of the total laminar flow resistance one-tenth is due to the pharynx, larynx, trachea and bronchi

Direct measurements of pressure and flow in the upper respiratory tract in man (Ferris, Opie & Mead, 1960) showed a curvilinear pressure–flow relationship, indicating the presence of turbulence, which was also inferred from model experiments by Ingelstedt and Toremalm (1960)

That there is a respiratory variation of the area of the glottic aperture is generally accepted during hyperventilation, but whether this occurs during resting ventilation is still under discussion Many authors (Negus, 1949, Fink, Basek & Epanchin, 1956) claim that the vocal cords abduct on inspiration and adduct on expiration even in resting ventilation These respiratory movements of the cords are ascribed fundamental importance for the regulation of the intrabronchial and the intrathoracic pressure, intrapulmonary gas distribution and cardiac output (Negus, 1949, Jackson & Jackson, 1959) Other investigators have questioned whether there are such respiratory movements during resting ventilation (Pressman & Kelemen, 1955, Carlens, 1960) On the basis of recent literature O'Neil (1959) refuted the opinion that the cords regulate the transalveolar pressure gradient The significance of the vocal cords for the respiratory function has been elucidated by O'Neil's studies on cases of recurrent nerve paralysis and in laryngectomized patients These two groups represent the two extremes as regards constriction of the airway at the level of the larynx Both groups had poor maximum breathing capacities, the cases of recurrent nerve paralysis increased functional residual capacities, the laryngectomized cases impaired intrapulmonary gas mixing

With the exception of those by Rattenborg *et al* (1961) direct measurements of the upper airway resistance have not revealed any difference between inspiratory and expiratory resistance (Ferris, Opie & Mead, 1960, Hyatt & Wilcox, 1961) Owing to a more powerful abduction of the vocal cords the resistance has been found to be smaller during hyperventilation

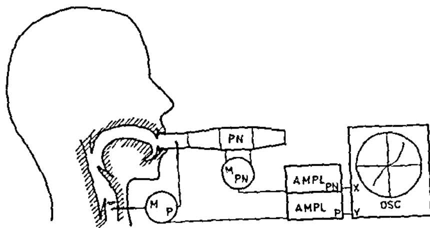


Fig 2 Experimental arrangement PN pneumotachograph, M_{PN}, pneumotachograph manometer with amplifier $AMPL_{PN}$ M_P manometer for measuring pressure difference between subglottic space and oral aperture by means of the amplifier, $AMPL_P$ and oscilloscope, *OSC*

ing on each side of the membrane At full scale deflection, however, there was a departure from linearity of 5–10%. To eliminate this source of error as far as possible only ±50% of the full-scale deflection of the electromanometer amplifier was used and further amplification was provided by the amplifier of the oscilloscope

The linearity of the pneumotachograph being acceptable, it sufficed to calibrate it against a flowrator at one point[1] The electrical integrator provided acceptable linear reproduction for at least 2 seconds.

Procedure

The cricothyroid membrane was punctured after injecting 1 ml of 1% Xylocaine This procedure does not involve any significant risk for the subject (Harken & Salzberg, 1948, Bonica, 1949) The plate supporting the puncture needle was affixed to the neck with sticking plaster. The space between the dental arches was kept the same in all subjects by means of mouth-pieces of identical dimensions The experiment was carried out with the subject in the sitting posture Flow and pressure difference or volume and pressure difference were recorded in a coordinate system on the oscilloscope When resting ventilation had been achieved the reproducibility was satisfactory Each exposure covered at least 2 tracings, 2 or 3 exposures from each experiment were used The subjects were then instructed to hyperventilate at an arbitrary rate

Records of the pressure flow curves were projected on millimetre paper

[1] Fisher Porter

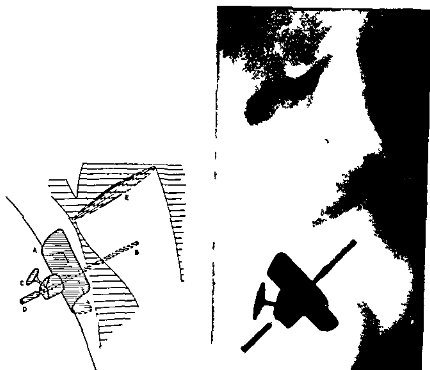


Fig. 1. Radiograph of soft tissues of the neck with the puncture needle inserted through the cricothyroid membrane. Inset: The position of the needle tip *B* in relation to the vocal cords *E*. *A*, the plate in contact with the skin. *C*, a set screw by which the needle is kept in the required position in relation to the plate. *D*, the nipple for the manometer tube.

(300 mm in length, 2 mm in internal diameter) to ensure the greatest possible fidelity. For the same reason the volumes of the pressure chambers of the inductance manometers were reduced by inserting Lucite rings on each side of the membrane.[1] The flow was measured with a Fleisch Model 2 pneumotachograph connected *via* Teflon tubes of the above type (100 mm in length) to a differential manometer identical with that described above. Volume was measured by electrical integration of the flow signal with an RC link having a 20-second time constant. The parameters were reproduced on an oscilloscope[2] and recorded photographically with a polaroid camera[3] (Fig. 2).

Calibration

The natural frequencies of the two oscillating systems for measurement of pressure gradients across the upper airways and for the pneumotachograph and manometer, at a damping of 0.36 and 0.33 respectively, were 23 and 27 cps. The two electromanometers gave symmetric readings for load-

[1] For this I am indebted to Mr. Aage Møller, Civ. Eng., Speech Transmission Laboratory, *Division of Telegraphy and Telephony*, Royal Institute of Technology, Stockholm, Sweden.

[2] Tectronix 502.

[3] Beatty.

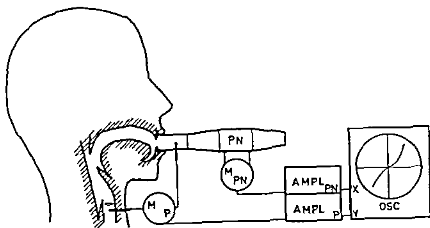


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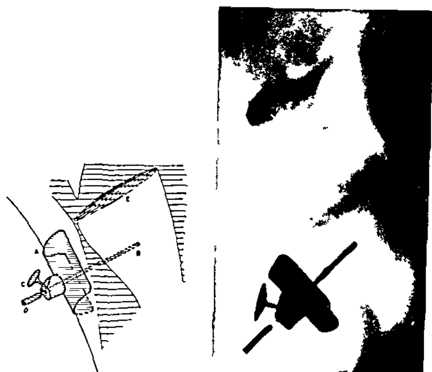


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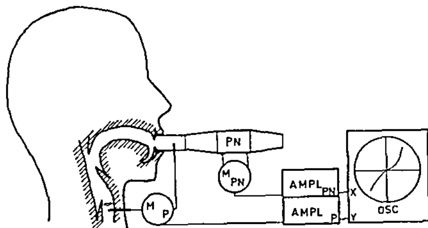


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The linearity of the pneumotachograph being acceptable it sufficed to calibrate it against a flowrator at one point[1] The electrical integrator provided acceptable linear reproduction for at least 2 seconds

Procedure

The cricothyroid membrane was punctured after injecting 1 ml of 1% Xylocaine This procedure does not involve any significant risk for the subject (Harken & Salzberg 1948 Bonica 1949) The plate supporting the puncture needle was affixed to the neck with sticking plaster The space between the dental arches was kept the same in all subjects by means of mouth pieces of identical dimensions The experiment was carried out with the subject in the sitting posture Flow and pressure difference or volume and pressure difference were recorded in a coordinate system on the oscilloscope When resting ventilation had been achieved the re producibility was satisfactory Each exposure covered at least 2 tracings, 2 or 3 exposures from each experiment were used The subjects were then instructed to hyperventilate at an arbitrary rate

Records of the pressure flow curves were projected on millimetre paper

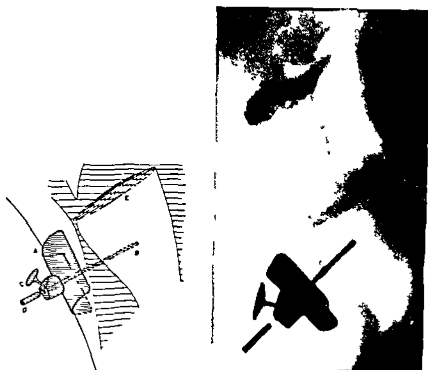


Fig. 1. Radiograph of soft tissues of the neck with the puncture needle inserted through the cricothyroid membrane. Inset: The position of the needle tip *B*, in relation to the vocal cords, *E*; *A*, the plate in contact with the skin; *C*, a set screw by which the needle is kept in the required position in relation to the plate; *D*, the nipple for the manometer tube.

(300 mm in length, 2 mm in internal diameter) to ensure the greatest possible fidelity. For the same reason the volumes of the pressure chambers of the inductance manometers were reduced by inserting Lucite rings on each side of the membrane.[1] The flow was measured with a Fleisch Model 2 pneumotachograph connected *via* Teflon tubes of the above type (100 mm in length) to a differential manometer identical with that described above. Volume was measured by electrical integration of the flow signal with an RC link having a 20-second time constant. The parameters were reproduced on an oscilloscope[2] and recorded photographically with a polaroid camera[3] (Fig. 2).

Calibration

The natural frequencies of the two oscillating systems for measurement of pressure gradients across the upper airways and for the pneumotachograph and manometer, at a damping of 0.36 and 0.33, respectively, were 23 and 27 cps. The two electromanometers gave symmetric readings for load-

[1] For this I am indebted to Mr. Aage Møller, Civ. Eng., Speech Transmission Laboratory, Division of Telegraphy and Telephony, Royal Institute of Technology, Stockholm, Sweden.

[2] Tektronix 502.

[3] Beatty.

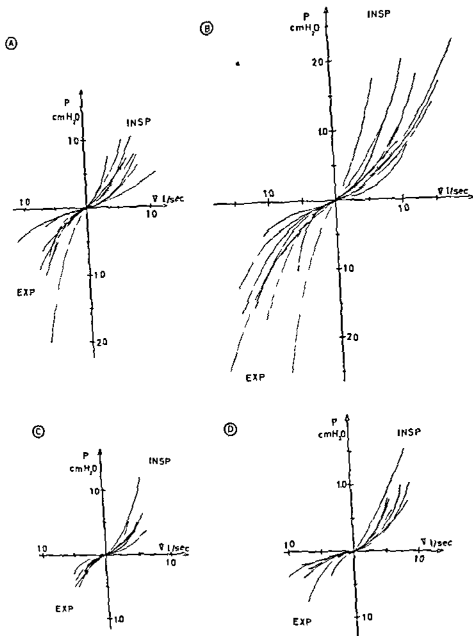


Fig. 3. Relationship between pressure drop across (*ordinates*), and flow through (*abscissae*) the upper airway. *A* men resting ventilation. *B* men hyperventilation. *C* women resting ventilation. *D* women hyperventilation.

parisons between men and women were made separately for each ventilatory phase and type of ventilation. For the comparison between two ventilatory phases the areas for each subject were compared in these phases, the differences were formed and the significance of the mean dif-

at a fourfold magnification and a mean curve for resting ventilation and hyperventilation was drawn for each subject. These curves were then transposed to a common scale. To the curves so obtained a second degree polynomial of the type $P = K_1\dot{V} + K_2\dot{V}^2$ was fitted. The values for the constants were obtained in the following way. The pressure–flow equations were integrated with respect to pressure from zero flow to 0.25 and 0.50 l/sec (see Appendix and Fig. 7). The numerical values of the integrals were also determined planimetrically and inserted in the integrated equations. The equations for the 0.25 and 0.50 l/sec integrals were solved for K_1 and K_2. As shown in the Appendix, the integrals or areas can also be ascribed a physical significance and they thus represent a characteristic quantity for the system. For the areas are proportional to the developed mean rate of work during an inspiration or expiration for a sinusoidal flow pattern with a mean flow equal to the maximum in the integration interval with a constant of proportionality of $4/\pi^2$.

Determination of mechanical work was carried out under identical conditions except that the electrical integrator was connected so that volume instead of flow was recorded. This gave closed loops, the area of which represented the product of ventilated volume and pressure difference between the larynx and the mouth, that is, the respiratory work performed in this segment of the airway. The area was determined with a planimeter and expressed in kpm/l of $\dot{V}_E$.

Comments

In model experiments it was found that deviant pressure values were obtained if the needle was at a very oblique angle instead of perpendicular to the airstream or if its tip was located in the posterior commissure. The former of these complications was avoided by keeping the needle perpendicular to the skin by means of the plate. Because of its length the needle probably reached the posterior wall of the larynx only in exceptional cases. In tests on man systematic changes in the position of the needle caused no noticeable variation in the shape of the pressure flow curves.

Statistical Methods

The material was divided into two groups according to sex, for each of which the inspiration and expiration curves were studied separately. By separating also the resting and hyperventilation studies 8 curve populations were obtained. For each of these the mean and the standard deviation for K_1 and K_2 were determined and a new polynomial was formed with the means of the constants. The comparison between different groups was made by comparing the integrals, i.e. the aforementioned areas obtained by planimetry. By testing for differences between the means of the respective areas male and female groups were compared. The com

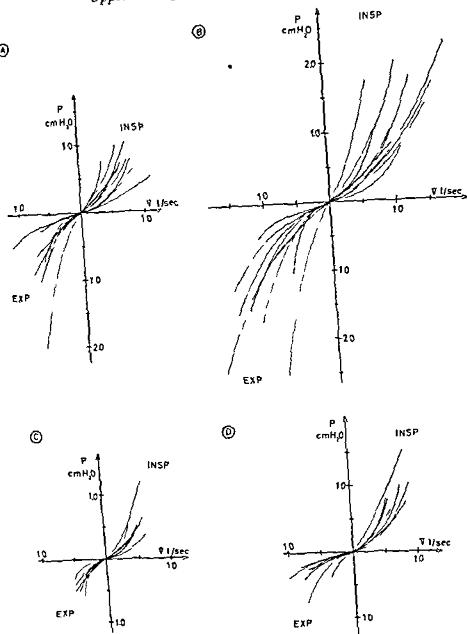


Fig. 3. Relationship between pressure drop across (*ordinates*) and flow through (*abscissae*) the upper airway. *A* men resting ventilation. *B* men hyperventilation. *C* women resting ventilation. *D* women hyperventilation.

parisons between men and women were made separately for each ventilatory phase and type of ventilation. For the comparison between two ventilatory phases the areas for each subject were compared in these phases, the differences were formed and the significance of the mean dif-

TABLE 1 *Inspiratory and expiratory pressure-flow integrals (l/sec × cm H_2O) determined planimetrically for flow intervals of 0–0.25 and 0–0.50 l/sec, coefficients for the second degree relationships between the pressure difference (cm H_2O) across, and flow (l/sec) through, the upper airway, and the mean rate of work (kpm/sec) developed by the passage of air through the upper airway at a mean flow of 0.50 l/sec, 10 men and 8 women*

	Inspiration					Expiration				
	0.25 l/sec ∫	0.50 l/sec ∫				0.25 l/sec ∫	0.50 l/sec ∫			
Subject	0 l/sec	0 l/sec	K_1	K_2	$E_{(0.50)}10^{-3}$	0 l/sec	0 l/sec	K_1	K_2	$E_{(0.50)}10^{-3}$
A *Resting ventilation*					MEN					
BS	0.014	0.202	1.20	0.62	4.99	0.020	0.102[a]	0.46	0.53	2.52
CGC	0.028	0.167	0.46	1.32	4.12	0.027	0.168	0.38	1.44	4.15
GP	0.023	0.138	0.37	1.10	3.41	0.023	0.160	0.19	1.63	3.95
NB	0.033	0.143	0.97	0.26	3.53	0.023	0.117	0.54	0.60	2.89
BE	0.053	0.626[a]	−1.62[b]	9.94	15.46	0.057	0.364	0.74	3.26	8.99
NBe	0.023	0.110	0.59	0.13	2.72	0.020	0.133	0.22	1.27	3.29
LLK	0.013	0.093	0.09	0.98	2.30	0.018	0.148	−0.0[illegible][b]	1.82	3.66
GK	0.012	0.050	0.37	0.05	1.24	0.012	0.033	0.50	−0.36[b]	0.82
AN	0.028	0.142[a]	0.66	0.72	3.51	0.010	0.018	0.26	0.19	1.19
GL	0.017	0.085	0.41	0.11	2.10	0.023	0.095	0.71	0.07	2.35
Mean	0.027	0.176	0.33	1.58	4.34	0.023	0.137	0.40	1.05	3.38
S.D.	±0.013	±0.163	±0.76	±2.96	±4.05	±0.013	+0.091	±0.24	±1.07	±2.26
					WOMEN					
UG	0.025	0.131[a]	0.53	0.82	3.31	0.018	0.160[a]	−0.13[b]	2.11	3.95
ML	0.032	0.293[a]	0.[illegible]0[b]	3.96	7.24	0.027	0.135[a]	0.65	0.65	3.33
GL	0.008	0.070	−0.05[b]	0.91	1.73	0.013	0.060	0.35	0.19	1.48
IH	0.025	0.135	0.52	0.84	3.33	0.020	0.117	0.34	0.89	2.89
IR	0.022	0.160	0.13	1.73	3.95	0.010	0.105	0.20[b]	1.56	2.59
AK	0.010	0.252	0.54	2.21	6.22	0.023	0.160[a]	−2.21[b]	8.83	11.36
DE	0.017	0.150[a]	−0.11[b]	1.97	3.71	0.027	0.20[illegible][a]	0.10	2.28	5.01
GO	0.027	0.128	0.70	0.48	3.16	0.030	0.157	0.82	0.41	3.[illegible]8
Mean	0.025	0.165	0.25	1.62	4.08	0.021	0.172	−0.04[b]	2.11	4.25
S.D.	±0.010	±0.072	+0.37	±1.13	+1.78	±0.007	+0.123	+0.95	+2.82	+3.05
B *Hyperventilation*					MEN					
BS	0.0[illegible]5	0.102	0.94	0.53	4.[illegible]0	0.017	0.097	0.[illegible]1	0.70	2.40
CGC	0.020	0.094	0.53	0.34	2.[illegible]2	0.015	0.083	0.25	0.70	2.20
GP	0.023	0.137	0.38	1.08	[illegible]	0.018	0.151	0.[illegible]8[b]	1.97	3.60
NB	0.022	0.094	0.66	0.14	2.[illegible]2	0.018	0.132	0.10	1.34	3.26
BI	0.067	0.352	1.17	2.02	8.69	0.053	0.311	0.90	2.[illegible]8	7.[illegible]8
NBe	0.017	0.065	0.57	−0.07[b]	1.61	0.010	0.047	0.20	0.17	1.11
LLK	0.015	0.068	0.42	0.19	1.68	0.013	0.065	0.31	0.51	1.[illegible]1
GK	0.022	0.097	0.63	0.22	2.40	0.010	0.0[illegible]5	0.[illegible]	0.12[b]	0.86
AN	0.007	0.040	0.13	0.29	0.99	0.017	0.107[a]	0.23	0.91	2.[illegible]
GL	0.018	0.073	0.57	0.02	1.80	0.023	0.112	0.53	0.48	2.77
Mean	0.025	0.118	0.63	0.38	2.92	0.019	0.115	0.32	0.90	2.81
S.D.	±0.017	±0.089	±0.36	±0.63	±2.21	±0.012	±0.078	±0.27	+0.80	±1.93

TABLE 1 *(continued)*

	Inspiration					Expiration				
Subject	0.25 l/sec ∫ 0 l/sec	0.50 l/sec ∫ 0 l/sec	K_1	K_2	$E_{(0.50)}$ 10⁻³	0.25 l/sec ∫ 0 l/sec	0.50 l/sec ∫ 0 l/sec	K_1	K_2	$E_{(0.50)}$ 10⁻³
					WOMEN					
LG	0.018	0.089	0.44	0.41	2.20	0.007	0.032	0.19	0.10	0.79
ML	0.022	0.175	0.01	2.09	4.32	0.008	0.043	0.17	0.26	1.06
GL	0.013	0.090	0.19	0.91	2.22	0.007	0.052	−0.03[b]	0.58	1.28
IH	0.018	0.132	0.10	1.44	3.26	0.010	0.043	0.30	0.07	1.06
ER	0.028	0.179	0.36	1.61	4.42	0.007	0.035	0.17	0.17	0.86
AK	0.048	0.217	1.34	0.60	5.36	0.027	0.228[a]	0.10[b]	2.88	5.63
DE	0.020	0.112	0.38	0.77	2.77	0.015	0.099	0.17	0.94	2.45
GO	—	—	—	—	—	—	—	—	—	—
Mean	0.024	0.142	0.40	1.12	3.51	0.012	0.076	0.12	0.71	1.88
S.D.	±0.012	±0.049	±0.44	±0.61	±1.22	±0.007	±0.071	±0.14	±1.00	±1.75

[a] Integrals determined from extrapolated curves

[b] In a rigid system negative values for the constants cannot exist It has not been possible so far to decide whether the negative values are due to inaccuracy in the binomial approximation or to a departure from rigidity of the system

ferences was tested by the *t* test (Snedecor, 1956) The differences between resting and hyperventilation for the corresponding phases were tested in a similar way

The mean and the standard deviation for mechanical work of breathing through the upper airway were determined for resting ventilation for men and women The differences between the means for men and women were tested Moreover the pressure difference for flow rates of 0.25 and 0.50 l/sec during resting ventilation and also 1.00 l/sec during hyperventilation was calculated or extrapolated for all subjects Means and standard deviations were calculated

RESULTS

In all subjects examined the relationship between pressure and flow was curvilinear and there was an appreciable dispersion between the curves (Fig 3 A D) The coefficients for the second degree polynomials fitted to these curves the pressure–flow integrals and the mean rate of work for a mean flow of 0.50 l/sec are given in Table 1 The mean equations are presented in Table 2 To facilitate comparison between the inspiratory and expiratory curves the latter have been moved from the third to the first quadrant (Fig 4 F H) It is evident from the figures that there was a difference between the shape of the inspiratory and expiratory pressure–flow curves only for women and only during hyperventilation Comparison between the pressure flow integrals revealed no difference between inspiration and expiration nor between men and women during resting ventilation

Table 1 *Inspiratory and expiratory pressure flow integrals (l/sec × cm H_2O) determined planimetrically for flow intervals of 0–0.25 and 0–0.50 l/sec, coefficients for the second degree relationships between the pressure difference (cm H_2O) across, and flow (l/sec) through, the upper airway, and the mean rate of work (kpm/sec) developed by the passage of air through the upper airway at a mean flow of 0.50 l/sec, 10 men and 8 women*

	Inspiration					Expiration				
Subject	$\int_{0\,l/sec}^{0.25\,l/sec}$	$\int_{0\,l/sec}^{0.50\,l/sec}$	k_1	k_2	$E_{(0.50)}10^{-3}$	$\int_{0\,l/sec}^{0.25\,l/sec}$	$\int_{0\,l/sec}^{0.50\,l/sec}$	k_1	k_2	$E_{(0.50)}10^{-3}$
A *Resting ventilation*					MEN					
BS	0.014	0.202	1.20	0.62	4.99	0.020	0.102[a]	0.46	0.53	2.52
CGC	0.028	0.167	0.46	1.32	4.12	0.027	0.168	0.38	1.44	1.15
GP	0.023	0.138	0.37	1.10	3.41	0.023	0.160	0.19	1.03	3.95
NB	*0.033*	*0.143*	*0.97*	*0.26*	*3.53*	0.023	0.117	0.54	0.60	2.89
BI	0.053	0.626[a]	−1.62[b]	9.94	15.46	0.057	0.364	0.74	3.26	8.99
NBe	0.023	0.110	0.59	0.43	2.72	0.020	0.133	0.22	1.27	3.29
LIK	0.013	0.093	0.09	0.98	2.30	0.018	0.148	−0.03[b]	1.82	3.66
GK	0.012	0.050	0.37	0.05	1.24	0.012	0.033	0.50	−0.30[b]	0.82
AN	0.028	0.142[a]	0.66	0.72	3.51	0.010	0.018	0.26	0.19	1.19
GI	0.017	0.085	0.41	0.41	2.10	0.023	0.095	0.71	0.07	2.35
Mean	0.027	0.176	0.33	1.58	4.34	0.023	0.137	0.40	1.05	3.38
S.D.	±0.013	±0.163	±0.76	±2.96	±4.05	±0.013	±0.091	±0.24	±1.07	±2.20
					WOMEN					
UG	0.025	0.131[a]	0.53	0.82	3.31	0.018	0.160[a]	0.13[b]	2.11	3.95
ML	0.032	0.293[a]	−0.[illegible]0[b]	3.96	7.24	0.027	0.135[a]	0.05	0.65	3.33
GI	*0.008*	*0.070*	*−0.05*[b]	*0.91*	*1.73*	*0.013*	*0.060*	*0.35*	*0.19*	*1.48*
IH	0.025	0.135	0.52	0.84	3.33	0.020	0.117	0.31	0.89	2.89
FR	0.022	0.100	0.13	1.73	3.95	0.010	0.105	0.20[b]	1.56	2.59
AK	0.010	0.252	0.54	2.21	6.22	0.023	0.400[a]	−2.21[b]	8.83	11.30
DI	*0.017*	*0.150*[a]	−0.11[b]	*1.97*	3.71	0.027	0.203[a]	0.10	2.28	5.01
GO	0.027	0.128	0.70	0.48	3.16	0.030	0.157	0.82	0.41	3.[illegible]8
Mean	0.025	0.165	0.25	1.62	4.08	0.021	0.172	0.04[b]	2.11	4.[illegible]
S.D.	±0.010	±0.072	±0.37	±1.13	±1.78	±0.007	±0.123	±0.95	±2.82	±3.05
B *Hyperventilation*					MEN					
BS	0.035	0.162	0.94	0.53	1.00	0.017	0.097	0.[illegible]1	0.70	2.40
CGC	0.020	0.094	0.53	0.[illegible]4	2.[illegible]2	0.015	0.089	0.[illegible]5	0.[illegible]0	2.20
GP	0.023	0.137	0.38	1.08	[illegible]8	0.018	0.151	0.08[b]	1.07	3.80
NB	0.022	*0.094*	0.60	*0.11*	2.[illegible]2	*0.018*	*0.132*	*0.10*	*1.11*	3.21
BI	0.067	0.352	1.47	2.02	8.09	0.053	0.311	0.30	2.[illegible]8	7.08
NBe	0.017	0.06[illegible]	0.57	0.07[b]	1.01	0.010	0.047	0.20	0.17	1.10
LIK	0.015	0.068	0.4[illegible]	0.19	1.08	0.013	0.065	0.31	0.[illegible]1	1.01
GK	0.022	0.097	0.63	0.22	2.40	0.010	0.0[illegible]5	0.[illegible]	0.12[b]	0.80
AN	0.007	0.040	0.13	0.29	0.99	0.017	0.107[b]	0.23	0.91	2.01
GI	0.018	0.073	0.57	0.0[illegible]	1.80	0.023	0.112	0.53	0.48	2.77
Mean	0.025	0.118	0.63	0.48	2.92	0.019	0.115	0.32	0.90	2.84
S.D.	±0.017	±0.089	±0.30	±0.63	±2.21	±0.012	±0.078	±0.27	±0.80	±1.93

TABLE 1 *(continued)*

	Inspiration					Expiration				
Subject	$\int_{0\ \mathrm{l/sec}}^{0\ 25\ \mathrm{l/sec}}$	$\int_{0\ \mathrm{l/sec}}^{0\ 50\ \mathrm{l/sec}}$	k_1	k_2	$E_{(0\ 50)}10^{-3}$	$\int_{0\ \mathrm{l/sec}}^{0\ 25\ \mathrm{l/sec}}$	$\int_{0\ \mathrm{l/sec}}^{0\ 50\ \mathrm{l/sec}}$	k_1	k_2	$E_{(0\ 50)}10^{-4}$
					WOMEN					
LG	0 018	0 089	0 44	0 41	2 20	0 007	0 032	0 19	0 10	0 79
ML	0 022	0 175	0 01	2 09	4 32	0 008	0 043	0 17	0 26	1 06
GL	0 013	0 090	0 19	0 91	2 22	0 007	0 052	−0 03[b]	0 58	1 28
IH	0 018	0 132	0 10	1 44	3 26	0 010	0 043	0 30	0 07	1 06
ER	0 028	0 179	0 36	1 61	4 42	0 007	0 035	0 17	0 17	0 86
AK	0 048	0 217	1 34	0 60	5 36	0 027	0 228[a]	0 10[b]	2 88	5 63
DE	0 020	0 112	0 38	0 77	2 77	0 015	0 099	0 17	0 94	2 45
GO	—	—	—	—	—	—	—	—	—	—
Mean	0 024	0 142	0 40	1 12	3 51	0 012	0 076	0 12	0 71	1 88
S.D	±0 012	±0 049	±0 44	±0 61	±1 22	±0 007	±0 071	±0 14	±1 00	±1 75

[a] Integrals determined from extrapolated curves

[b] In a rigid system negative values for the constants cannot exist It has not been possible so far to decide whether the negative values are due to inaccuracy in the binomial approximation or to a departure from rigidity of the system

ferences was tested by the *t* test (Snedecor, 1956) The differences between resting and hyperventilation for the corresponding phases were tested in a similar way

The mean and the standard deviation for mechanical work of breathing through the upper airway were determined for resting ventilation for men and women The differences between the means for men and women were tested Moreover the pressure difference for flow rates of 0 25 and 0 50 l/sec during resting ventilation and also 1 00 l/sec during hyperventilation was calculated or extrapolated for all subjects Means and standard deviations were calculated

RESULTS

In all subjects examined the relationship between pressure and flow was curvilinear and there was an appreciable dispersion between the curves (Fig 3 A D) The coefficients for the second degree polynomials fitted to these curves, the pressure flow integrals and the mean rate of work for a mean flow of 0 50 l/sec are given in Table 1 The mean equations are presented in Table 2 To facilitate comparison between the inspiratory and expiratory curves the latter have been moved from the third to the first quadrant (Fig 4 E H) It is evident from the figures that there was a difference between the shape of the inspiratory and expiratory pressure-flow curves only for women and only during hyperventilation Comparison between the pressure-flow integrals revealed no difference between inspiration and expiration nor between men and women during resting ventilation

TABLE 2. *Equations derived from means of coefficients for the second degree relationships between the pressure difference (cm H_2O) across and flow (l/sec) through the upper airway, 10 men and 8 women*

	Resting ventilation		Hyperventilation	
	Inspiration	Expiration	Inspiration	Expiration
Men	$P = 0.33\,\dot{V} + 1.58\,\dot{V}^2$	$P = 0.40\,\dot{V} + 1.05\,\dot{V}^2$	$P = 0.63\,\dot{V} + 0.48\,\dot{V}^2$	$P = 0.32\,\dot{V} + 0.90\,\dot{V}^2$
Women	$P = 0.25\,\dot{V} + 1.62\,\dot{V}^2$	$P = -0.04\,\dot{V} + 2.11\,\dot{V}^2$	$P = 0.40\,\dot{V} + 1.12\,\dot{V}^2$	$P = 0.12\,\dot{V} + 0.71\,\dot{V}^2$

up to a flow of 0.50 l/sec. During hyperventilation there was no difference between the sexes, nor between inspiration and expiration for men. Inspiratory pressure–flow integrals for women during hyperventilation were significantly larger than the expiratory [0–0.25 l/sec ($P < 0.01$) and 0–0.50 l/sec ($P < 0.05$)]. Pressure–flow integrals were larger during resting ventilation than during hyperventilation for men only during expiration and only

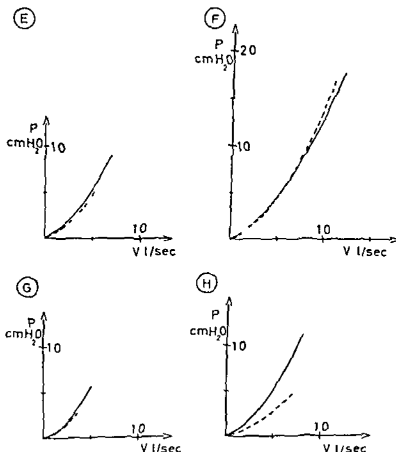


Fig. 4. Comparison between inspiration (*continuous lines*) and expiration (*broken lines*). *E* men resting ventilation. *F* men hyperventilation. *G* women resting ventilation. *H* women hyperventilation. Curves plotted from mean equations.

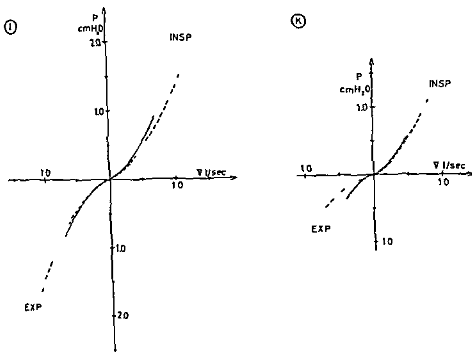


Fig 5 Comparison between resting ventilation (*continuous lines*) and hyperventilation (*broken lines*) *I* men *K* women Curves plotted from mean equations

for flow values of 0–0 25 l/sec ($P < 0.05$) Also for women the integrals were significantly larger during resting ventilation, but only during expiration [0 0 25 l/sec ($P < 0.05$) and 0–0 50 l/sec ($P < 0.01$)] (Fig 5 I–K, Fig 6 L–M) For a flow rate of 0 5 l/sec the upper airway resistance was 1 0 and 0 8 cm H O/l/sec during resting ventilation and hyperventilation respectively During hyperventilation it was 1 2 cm H O/l/sec for a flow rate of 1 0 l/sec

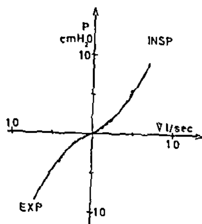
The mean pressure differences and their standard deviations at flow rates of 0 25 0 50 and 1 00 l/sec were calculated for men and women during inspiration and expiration during resting ventilation and hyperventilation The results are presented in Table 3 For the same flow rate the pressure differences fall within a narrow range except the expiratory values for women at all three flow rates during hyperventilation

The mechanical work performed in driving air through the upper airway was 0 008 kpm/l of V_E for men and 0 006 kpm/l of V_E for women (Table 4)

DISCUSSION

Methods

The pneumotachograph was calibrated with inspiratory air, this differs from expiratory air as regards temperature humidity and oxygen and carbon dioxide contents The Mead Silverman pneumotachograph is very



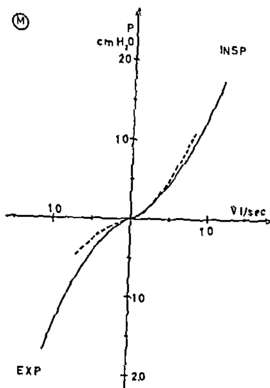


Fig. 6. Comparison between men (*continuous lines*) and women (*broken lines*). *L*, resting ventilation; *M*, hyperventilation. Curves plotted from mean equations.

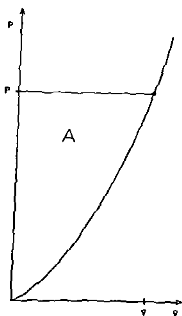


Fig. 7. Pressure flow curve integrated with respect to pressure (P) from zero flow to V_1. The integral is represented by the area A enclosed by the curve, a horizontal line through the point $P_1 V_1$ and the ordinate.

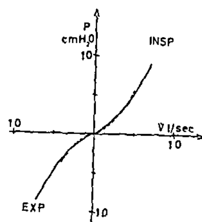
TABLE 3 *Means and standard deviations of inspiratory and expiratory pressure difference (cm H_2O) across the upper airway for flow rates of 0.25, 0.50 and 1.00 l/sec, 10 men and 8 women*

Flow rate l/sec	Resting ventilation				Hyperventilation			
	Inspiration		Expiration		Inspiration		Expiration	
	Men	Women	Men	Women	Men	Women	Men	Women
0.25	0.19 ±0.08	0.16 ±0.07	0.16 ±0.08	0.12 ±0.08	0.19 ±0.12	0.17 ±0.09	0.14 ±0.09	0.08 ±0.04
0.50	0.57 ±0.42	0.53 ±0.21	0.46 ±0.29	0.51 ±0.27	0.44 ±0.31	0.48 ±0.18	0.39 ±0.25	0.24 ±0.20
1.00	—	—	—	—	1.11 ±0.91	1.52 ±0.50	1.2[illegible] ±0.87	0.84 ±0.90

TABLE 4 *Mechanical work W (kpm/l of V_E) performed to move air through the upper airway during resting ventilation 9 men and 8 women*

Men			Women		
Subject	W	Tidal volume	Subject	W	Tidal volume
BS	0.008	0.6	LC	0.003	0.6
CGC	0.015	0.7	MI	0.004	0.4
CI	0.010	0.7	CI	0.003	0.6
NB	0.009	0.6	HH	0.003	0.5
RE	0.012	0.7	LR	0.003	0.5
CCK	0.004	[illegible]	AK	0.012	0.6
GK	0.005	1.0	DI	0.007	0.6
AN	0.005	0.7	GO	0.008	0.7
CL	0.005	0.7	—	—	—
Mean	0.008	0.7		0.006	0.6
SD	±0.004	±0.1		±0.003	±0.1

insensitive to variations in oxygen and carbon dioxide contents (*Fritts et al* 1959), in view of the similarity of the instruments it is reasonable to suppose that also the sensitivity of the Fleisch model to these variations is negligible. During its passage through the pneumotachograph the room air was gradually heated to 26 C. Since the influence of this gradual rise in temperature on the volume is difficult to assess, no correction was attempted. A rise from 22 to 35°C results in an increase in viscosity of 3.5% (Fleisch 1956), which is negligible in this [illegible] on. The difference in [illegible] nished by the heater, [illegible] inspired and expired



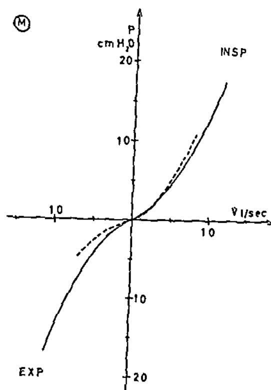


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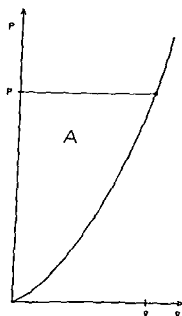


Fig. 7. Pressure flow curve integrated with respect to pressure (*P*) from zero flow to $\dot{V}$. The integral is represented by the area *A* enclosed by the curve, a horizontal line through the point $P_1/\dot{V}_1$ and the ordinate.

ZUSAMMENFASSUNG

Der Strömungswiderstand in den oberen Luftwegen, gemessen als Beziehung von Druckabfall in und Strömungsgeschwindigkeit durch die oberen Luftwege, wurde bei 10 Männern und 8 Frauen bestimmt. Der Druckabfall wurde direkt durch Punktion der Membrana Cricothyreoidea gemessen. Die Beziehung zwischen Druckabfall und Strömungsgeschwindigkeit war bei In- wie Exspiration und bei Ruheatmung wie Hyperventilation kurvenlinear. Das deutet demnach auf eine turbulente Strömung hin. Alle Kurven können als Gleichungen zweiten Grades ausgedrückt werden.

Der Strömungswiderstand während Ruheatmung war etwas grösser als bei Hyperventilation, was besonders bei Frauen und der Exspiration bemerkbar war. Der mittlere Strömungswiderstand der oberen Luftwege betrug bei einer Strömungsgeschwindigkeit von 0.5 l/sec 1.0 cm H_2O/l/sec bei Ruheatmung. Bei Hyperventilation betrug er 0.8 und 1.2 cm H_2O/l/sec bei Strömungsgeschwindigkeiten von 0.5 und 1.0 l/sec. Der Strömungswiderstand der oberen Luftwege macht etwa die Hälfte des gesamten Atemwiderstandes aus. Die mechanische Arbeit, die Luft durch die oberen Atemwege zu befördern, wurde als Produkt des Atemvolumens und des Druckabfalls berechnet. Bei Ruheatmung betrug sie 0.008 für Männer und 0.006 kpm/l V_E für Frauen.

APPENDIX

(C. G. *Allander, Professor of Heat Technology, Royal Institute of Technology, Stockholm, and H. Schiratzki, Department of Otolaryngology, Karolinska Sjukhuset, Stockholm*)

The pressure–flow integral has the following form

$$A = \int_0^p V\, dp \qquad [1]$$

With the approximation made

$$p = k_1 V + k_2 V^2 \qquad [2]$$

A may then be written

$$A = \int_0^V (k_1 V + 2k_2 V^2)\, dV \qquad [3]$$

which on integration gives

$$A = \frac{V_1}{2}(k_1 V_1 + \tfrac{4}{3} k_2 V_1^2) \qquad [4]$$

If it is assumed that the respiratory flow is sinusoidal in form, it may be expressed by the relation

$$V(t) = \frac{V_T}{2}\left\{1 + \sin 2\pi \frac{t}{T}\right\} \qquad [5]$$

where V_T *is the inspired volume and* T the time for a complete respiratory cycle. Differentiating with respect to time we obtain

For a flow rate of 0.5 l/sec the upper airway resistance was 1.0 and 0.8 cm H_2O/l/sec during resting ventilation and hyperventilation respectively. During hyperventilation it was 1.2 cm H_2O/l/sec for a flow rate of 1.0 l/sec.

Total airway resistance determined with a body plethysmograph is 1.5 ± 0.9 cm H_2O/l/sec measured at a flow of 0.5 l/sec panting 2 cps and at functional residual capacity (Briscoe & DuBois 1958). If measurements of resistance with the present technique are comparable with plethysmographic ones, then the present mean of 0.8 cm H_2O/l/sec (hyperventilation, this type of breathing regarded as most comparable to panting) constitutes 53% of the total airway resistance.

The difference between inspiratory and expiratory resistance demonstrated by Rattenborg *et al.* (1961) was not confirmed in this study. This does not exclude the possibility of an adduction of the cords on expiration. As similarity between the resistance in inspiration and expiration does not necessarily mean that the vocal cords do not move between the two phases. For in animal experiments Campbell *et al.* (1963) found that for glottic chinks of equal dimensions the resistance in inspiration exceeds that in expiration, a fact they ascribe to a more favourable aerodynamic form of the larynx in the direction for expiration.

Determination of upper respiratory mechanical work

Total respiratory mechanical work has been reported to be of the order of 0.03–0.05 kpm/l of V_T (Otis 1954). The observed mean of 0.007 kpm/l of V_T for upper respiratory mechanical work is then 14–23% of the total.

Seventy per cent of the total mechanical work of respiration is dissipated in overcoming the elastic resistance (Otis 1954). For a moderate flow the airway resistance is only about 20% of the nonelastic resistance (Cherniack & Cherniack 1961). It may be assumed from this that the portion of the respiratory mechanical work expended in overcoming the total airway resistance amounts to only about 6% of the total. The discrepancy between this value and the comparatively high observed values of 14–23% may be accounted for by the difficulty in determining the total respiratory mechanical work. If instead the values of 0.8–1.0 kpm/min are assumed for the total respiratory mechanical work (Cherniack & Cherniack 1961) and the ventilation is taken as 6.1 l/min, the observed respiratory mechanical work in the upper airways is 1.5–5% of the total. From the values given in Table 1 it is evident that for a mean flow of 0.50 l/sec the mean rate of work developed in the upper airways is 0.004 kpm/sec. This yields a value of 0.010 kpm per breath assuming a duration of 2.5 sec for the breathing period. From the method utilizing the pressure-volume product a value of 0.004 kpm is obtained for a tidal volume of 0.5 l. Thus the two methods give values of comparable magnitude.

$$R_m \quad \frac{\pi^2}{4}\frac{A}{\dot{V}_m^2} = \frac{\pi^2}{4}\frac{A}{\dot{V}_1^2}. \qquad [16]$$

Hence if it is assumed that the flow is sinusoidal the mean resistance is directly proportional to the area A, and if $\dot{V}_1$ is the same for all subjects, their mean resistances will be directly comparable

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... n menschlichen Atemwegen und der

$$\dot{V} = \pi \frac{V_T}{T} \cos 2\pi \frac{t}{T} \qquad [6]$$

The respiratory work for inspiration is expressed by the integral

$$W_{in} = \int_a^b p \dot{V} \, dt, \qquad [7]$$

where the limits a and b are the times for the beginning and end of inspiration. From [5] it is seen that these limits are $\pm T/4$. Inserting [2] and [6] in [7], we have

$$W_{in} = \int_{T/4}^{T/4} \left\{ K_1 \pi \frac{V_T}{T} \cos 2\pi \frac{t}{T} + K_2 \pi^2 \left(\frac{V_T}{T}\right)^2 \cos^2 2\pi \frac{t}{T} \right\} \pi \frac{V_T}{T} \cos 2\pi \frac{t}{T} \, dt \qquad [8]$$

On integration we have

$$W_{in} = \left(\frac{\pi V_T}{T}\right)^2 \frac{T}{4} \left(K_1 + \tfrac{8}{3} K_2 \frac{V_T}{T}\right) \qquad [9]$$

The mean flow $\dot{V}_m$ during inspiration is

$$\dot{V}_m = \frac{2 V_T}{T}, \text{ whence } T = \frac{2 V_T}{\dot{V}_m} \qquad [10]$$

Substituting for T in [9] we have

$$W_{in} = \frac{\pi^2}{8} V_T (K_1 \dot{V}_m + \tfrac{4}{3} K_2 \dot{V}_m^2) \qquad [11]$$

The quantity W_{in} is the work done in inspiration. On dividing this by the time for one inspiration we obtain the mean rate of work, E_m. That is,

$$E_m = \frac{2 W_{in}}{T} \qquad [12]$$

which, with [10] and [11], gives

$$E_m = \frac{\pi^2}{8} \dot{V}_m (K_1 \dot{V}_m + \tfrac{4}{3} K_2 \dot{V}_m^2) \qquad [13]$$

On comparing [13] with [4] it is seen that if $\dot{V}_m$ is put equal to V_1, we have

$$A = \frac{4}{\pi^2} E_m \qquad [14]$$

The mean resistance on inspiration may be defined as

$$R_m = \frac{E_m}{\dot{V}_m^2} \qquad [15]$$

Inserting the expression for E_m from [14], we have

QUANTIFICATION OF THE HUMAN NYSTAGMIC RESPONSE TO ANGULAR ACCELERATION PREDICTION FORMULAE AND NOMOGRAPH

JAMES H BROWN and GEORGE H CRAMPTON
Fort Knox, Ky, U.S.A

From the U.S Army Medical Research Laboratory Fort Knox

Five young adult men with normal labyrinthine function were stimulated by a series of graded angular accelerations, during which they carried out particular mental tasks Each subject was seated at the center of rotation eyes open and with head fixed with a bite board so that the lateral canals were in the horizontal plane of rotation The subject was enclosed in a capsule which provided a totally dark environment, and shielded him from wind currents Low level masking noise and vibration prevented detection of extraneous cues related to angular velocity Ocular nystagmus was analyzed second by second and an empiric equation fitted to the data

The semicircular canal system has been compared by analogy to a critically damped torsion pendulum (van Egmond Groen & Jongkees, 1949, Mayne 1950) Attempts have been made to evaluate the equation constants for elasticity friction and mass by employing data from both man and lower animal Results of work with this formulation have been fruitful, but it is commonly recognized that there are at least three striking disparities between predictions from the torsion pendulum analog and the data (*a*) A linear relationship between the magnitude of the stimulus and the magnitude of the response is predicted This is an unusual prediction for the behavior of any sense organ and, in fact, a nonlinear relationship is found for the human nystagmic response (*b*) The equation constants which are determined for periods of constant velocity after an acceleration should also fit the development of the response during the acceleration The finding is that different constants are required if each segment is to be closely fitted (*c*) The analog does not allow for the influence of the arousal level of the subject Recent findings (e g Collins, Crampton & Posner 1961, Collins 1962) have shown that the magnitude of the nystagmic response is systematically influenced by the status of arousal or alertness of the test subject

The purpose of this experiment was to collect precise human nystagmic data and then to provide a systematic formulation such that it would be

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Fig. 1 Rotatory stimulator with the capsule removed. Note the firm restraining chair, head rest and bite board arrangement that serve to prevent extraneous stimulation due to head movement. The electrodes are taped to the skin, and the wires lead to the patch panel over the subject's head and thence to slip rings.

The alertness states were initiated and maintained by precise instructions as follows: (*a*) A mental arithmetic instruction (MA) required the subject to rapidly and continuously perform one of two problems. Either divide a given number and each successive quotient by 5, more precisely $X/5^n$, or perform successive multiplications by raising a given number to the *n*th power thusly, X^n. Answers were recorded. (*b*) A psychophysical judgment instruction (KP) required the subject to indicate his subjective velocity by pressing the signal key every time he believed he had passed through a 90° arc. (*c*) A reverie instruction (REV) called upon the subject to ignore the environment, relax, but keep his eyes open and his head positioned.

Five angular accelerations of 9.0-sec duration were employed. The values of 3.0, 5.0, 8.0, 12.0 and 17.0°/sec² were programmed such that their velocity

possible to predict man's nystagmic response to a wide range of acceleration and stimulus duration combinations. The torsion pendulum analogy was abandoned, and an empiric formulation is offered.

METHODS

Stimulator

The hydraulically driven angular accelerator consists of a pedestal which mounts a vertical spindle upon which a rotating crossbeam provides support for the subject's chair. Although the chair may be displaced at a radius of up to one meter from the axis of rotation, it was positioned for this experiment, so that the subject's head was over the rotatory axis. The driving machinery is below the floor of the rotating beam room, and control and recording apparatus are in an adjoining control room. This rotatory device is capable of smooth and accurate constant accelerations from 0.01°/sec² to 50.0°/sec² to terminal velocities of 300°/sec in either a clockwise (CW) or counterclockwise (CCW) direction. A notable feature of this device, and one employed for these observations, is the capability for accelerating through zero velocity without a discernible transient. Thus *accelerative stimuli which produce velocity programs that are symmetrical about zero velocity can be programmed.*

An adjustable bite board restrained the subject's head in a fixed position over the axis of rotation (Fig. 1). Not shown in this figure is the capsule which entirely enclosed the subject, permitted control of visual stimulation, and eliminated cues of angular velocity associated with air movement across the face. A ventilating fan for the capsule interior, and a small "dither" motor provided masking vibration and noise at a low, but yet sufficient level to prevent detection of extraneous signals coupled to actual machinery rotation. Electronic voice intercommunication between subject and operator was provided.

Recording

Electrodes were taped near the outer canthi of the eyes, and an indifferent electrode placed in the center of the forehead. These electro-oculographic signals for horizontal eye movements were led through slip rings to an Offner Type-T ink-writing recorder in the adjacent control room. Eye movement potentials were amplified with a 1.4 sec RC time constant and displayed with a 25 mm/sec paper speed. The periods of acceleration and signals the subject initiated by pressing a key also were recorded.

Procedure

All testing was conducted in total darkness and each subject instructed to keep his eyes open and directed straight ahead. Five subjects were given a counterbalanced series of stimulations which included five intensities of angular acceleration and three mental alertness states.



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Five angular accelerations of 9 0-sec duration were employed The values of 3 0, 5 0, 8 0, 12 0 and 17 0°/sec² were programmed such that their velocity

schedules were symmetrical about zero velocity. For example, a subject would be initially accelerated subthreshold until he reached a specified base velocity. For 8.0°/sec² this base velocity would be 6.0 rpm in a CCW direction. The first suprathreshold trial of 8.0°/sec² magnitude and 9.0 sec duration would carry the subject through zero velocity and to a terminal velocity of 6.0 rpm in a CW direction. After a period of 5 min, the next acceleration, negative in sign, would return the subject to the base CCW velocity of 6.0 rpm. Each acceleration is hereafter referred to as a trial.

This symmetrical velocity program is especially critical for nystagmus work because arousal is of importance. It is frequently found that subjects are more excited on trials of increasing velocity than on trials of decreasing velocity and consequently produce more nystagmus on the former than on the latter. The symmetrical program avoids this complication.

Equally important is the length of the interval between accelerations. Since secondary nystagmic responses frequently are recorded for 3–4 min following accelerations of this magnitude, 5 min of constant velocity were allowed between all trials.

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Calibration

Prior to the preliminary trial and again following the last acceleration trial, each subject was instructed to fixate a center light, and then on command sharply move his eyes to a light displaced 10° to the right from center, return his gaze to the center, shift his eyes smartly to a third light displaced 10° to the left of center and then recenter his eyes. Several repetitions of this maneuver were recorded.

RESULTS

All data were reduced by hand measurement. The vertical magnitude of the slow phase sweep of each primary nystagmic beat was measured first

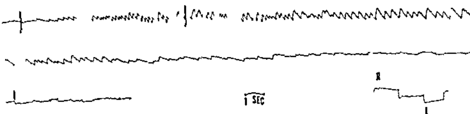


Fig. 2. Nystagmic response to a 17.0°/sec² positive acceleration of 9.0 sec duration with the subject performing mental arithmetic. The period of acceleration is indicated between the vertical marks: fast phase to the right (up) and the end of the primary and onset of the secondary nystagmus is shown by the arrow. The secondary nystagmus continued for several seconds beyond the sample. Calibrations of 10° right and left eye movements and the time scale are shown.

in mm for each one second segment of the record and then converted to degrees for each second according to the calibration obtained at the end of each session. A recording example is in Fig. 2.

Consideration of the variability and dispersion of nystagmic data from cat and man has led us to conclude that geometric means are a more appropriate measure of central tendency than arithmetic means. Accordingly geometric means were computed for each second of primary nystagmus during the entire period of acceleration and constant velocity for each of the fifteen combinations of acceleration and instruction. Each mean includes data from both positive and negative accelerations.

Extended examination of the data with attempts at curve fitting indicated that the critically damped torsion pendulum analog model did not fit the data. Certainly segments of the function would offer respectable fits but the analog fails to represent a wide range of acceleration magnitudes or even the transition from a period of acceleration to the subsequent constant velocity. It was therefore decided to set aside a theoretic model approach and to determine an empiric equation which would fit the data and offer the utility of prediction for nystagmic responses.

It is unnecessary to detail the approximation procedures required to fit empiric curves and we will proceed to the final result. The magnitude of the nystagmic slow phase reaction during acceleration is given by

$$\theta = \Psi \alpha^k \ln_e[(t_1 + c)/c] - T \qquad (1)$$

where

θ nystagmic output in degrees/sec of slow phase excursion (only for $\theta \geq 0$)
α constant angular acceleration in degrees/sec²
t_1 time in sec of acceleration from time of onset
Ψ 2.1 for MA, 1.8 for KP and 1.4 for RLX = coefficient reflecting the mental tasks
k 0.66 = slope constant relating power function between θ and α
T = 5 = arbitrary constant, and
c = 1.8 = an arbitrary constant

schedules were symmetrical about zero velocity. For example, a subject would be initially accelerated subthreshold until he reached a specified base velocity. For 8.0°/sec², this base velocity would be 6.0 rpm in a CCW direction. The first suprathreshold trial of 8.0°/sec² magnitude and 9.0-sec duration would carry the subject through zero velocity and to a terminal velocity of 6.0 rpm in a CW direction. After a period of 5 min, the next acceleration, negative in sign, would return the subject to the base CCW velocity of 6.0 rpm. Each acceleration is hereafter referred to as a trial.

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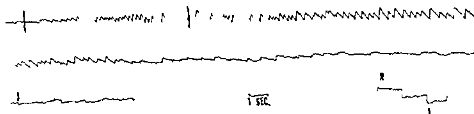


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α constant angular acceleration in degrees/sec²
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q 21 for MA 18 for KP and 14 for RLV = coefficient reflecting the mental tasks
k 0.66 slope constant relating power function between θ and α
T arbitrary constant and
c = 18 = an arbitrary constant

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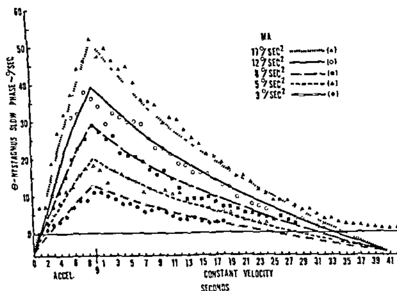


Fig. 4 The data from Fig 3 plotted in linear units on both scales The responses of less than 2° sec are plotted for the 17° sec² acceleration and the prominence of the "tail" is representative for all conditions A substantial proportion of the "tail" is due to random eye movements or "noise" and this fact clearly points out the difficulty of using the duration of nystagmus as a criterion of response magnitude

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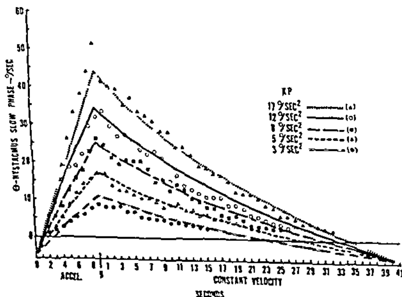


Fig. 5 Responses to accelerations when subjects perform the key pressing (KP) task

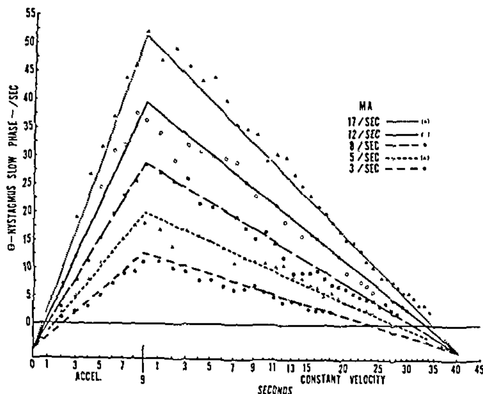


Fig. 3. Averages of the second-by-second responses plotted against the non-linear time abscissa described in the text. The mental arithmetic (MA) task was performed throughout each trial. Responses from positive and negative accelerations are added together and no slow phase response of less than 2°/sec is plotted.

The magnitude of the nystagmic slow-phase reaction during a period of constant velocity following an acceleration is given by

$$\theta = \theta' - p(\theta' + T)\ln_e[(t_2+c)/c], \qquad (11)$$

where θ, T, and c have the same values as during acceleration, $\theta > 0$, and

θ' = nystagmic output in degrees/sec of slow phase excursion at the end of the acceleration

t_2 = time in sec of constant velocity from the end of the acceleration, and

p = 0.85 = an arbitrary constant

Fig. 3 shows how well this function fits when nystagmic output θ is plotted against the non-linear abscissa ($\ln[t+c] - \ln c$) for the mental arithmetic condition. Figs. 4, 5 and 6 show the data plotted against a linear time base. By and large, the formulation, and the constants given above fit the data over this wide range of stimuli and systematically allow for the influence of mental activity on nystagmic output.

DISCUSSION

An examination of the formulation offered here reveals two important features. It is seen that there is a power function relationship between the

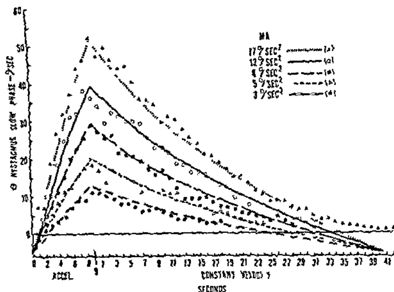
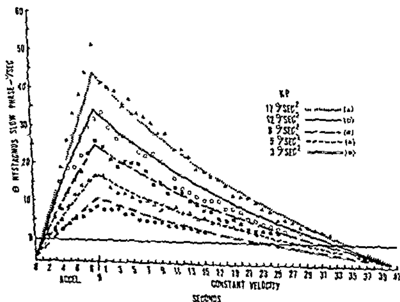


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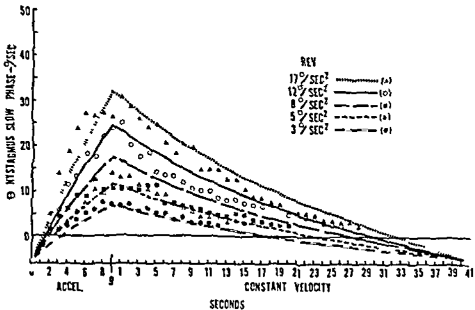


Fig. 6. Responses to acceleration when subjects follow the reverie (REV) instruction. The reverie instruction is not very precise and more variability in the response is characteristic.

important in determining output during acceleration, it is not a factor during the recovery in the following period of constant velocity. In fact the rate of recovery is a function only of the magnitude of the nystagmic output at the end of the acceleration.

These formulations are rather unwieldy for rapid computation and their ready utility for prediction of nystagmic responses is appreciably lessened. For this reason a nomograph has been prepared (Fig. 7) by which the nystagmic response may be rapidly determined for a wide range of intensities and durations. It is important to restate the conditions employed to

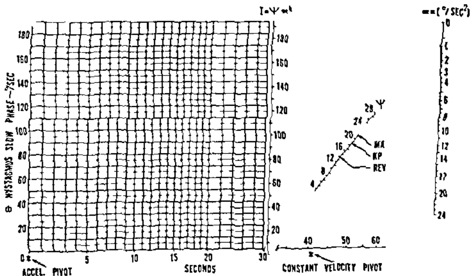


Fig. 7. Nomograph for determining nystagmic response.

obtain the data on which the nomograph is based The data applies to young adult human subjects with moderate acceleration experience, with eyes open but in total darkness riding at the center of rotation with head fixed in a bite board and the lateral canals fixed in the horizontal plane of rotation Further very specific mental tasks were included in instructions for the subjects and the method of calibration was specified Angular accelerations were of constant magnitude throughout their duration

To determine the predicted value of nystagmic output from the nomograph during any constant acceleration of a given magnitude and duration first determine the *I* or index value This is done by projecting a line from the appropriate α value through the specified Ψ value and determining the correct index point by noting the point of intersection at the *I* line Connect this point on the index line to the acceleration pivot point in the lower left hand corner of the nomograph Nystagmic output in degrees per second may now be determined from the ordinate at the left for any time during the application of the acceleration as indicated on the abscissa

A similar procedure is to be followed for a period of constant velocity following an acceleration First note the amount of nystagmic output at the end of the acceleration A straight line between that point on the ordinate to the left and the constant velocity pivot point will permit the rapid determination of the nystagmic output for anytime following the cessation of the acceleration

Our own experience with this nomograph has shown that the most frequent adjustment needed from one set of data to another involves the Ψ constant Even here the required adjustments are quite small indeed and probably vary according to the individual differences in performing the tasks The most obvious factor not accounted for in the expressions herein offered is that of the habituation of this response (Crampton 1964) These subjects might best be described as moderately habituated and the rapid response decline that is often seen over the first few exposures to acceleration did not intrude on these data Just how the habituation variable might be included in this formulation is a matter for further work but it is not too unlikely that it will operate much like Ψ

Although a theoretic equation in which the constants can be determined from a source other than the immediate data is esthetically and practically more desirable than an empiric formulation such as offered here there are two advantages to this presentation First it will predict nystagmic output over the range of values from which it was derived Second it offers a precise description of the behavior of the vestibulo ocular response and provides a sound basis for new attempts to construct a theoretic equation with biologically referable constants

ZUSAMMENFASSUNG

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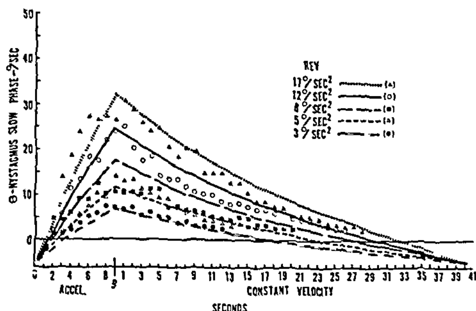


Fig 6 Responses to acceleration when subjects follow the reverie (REV) instruction The reverie instruction is not very precise, and more variability in the response is characteristic

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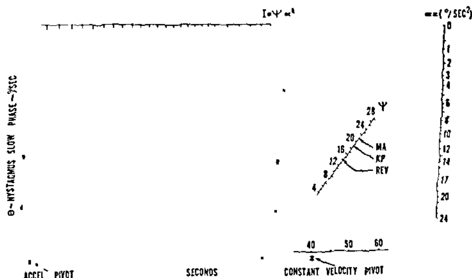


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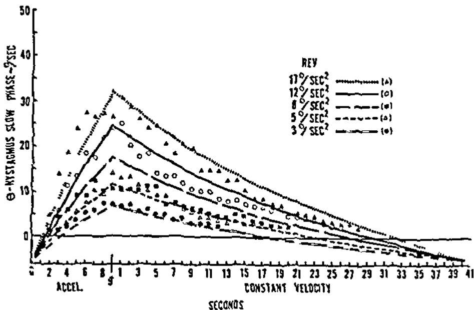


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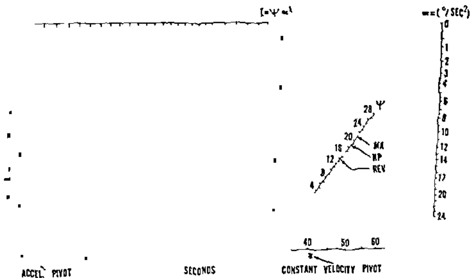


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bestimmte geistige Aufgaben ausfuhrten Jede Versuchsperson sass im Drehungszentrum mit offenen Augen, und der Kopf wurde mit einem zwischen die Zähne geklemmten Stab derart festgehalten dass die Seitenkanäle in der horizontalen Drehungsebene lagen Die Versuchsperson wurde in einer Kapsel eingeschlossen welche eine völlig dunkle Umgebung erzeugte und vor Luftströmungen schützte Leises maskierendes Geräusch und Vibrierung verhüteten die Entdeckung von äusseren mit der Drehungsgeschwindigkeit zusammenhängenden Eindrücken Okulärer Nystagmus wurde jede Sekunde analysiert und eine empirische Gleichung den Daten angepasst

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